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JANUARY, 1933

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, Jan. 20, 1926, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in the Act of Feb. 28, 1925, authorized Jan. 27, 1926.

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ARCHIVES OF PATHOLOGY

VOLUME 15 JANUARY, 1933 NUMBER 1

FATE OF ENDOMETRIAL EMBOLI IN THE VENOUS CIRCULATION OF THE RABBIT

VICTOR C. JACOBSEN, M.D.

ALBANY, N. Y.

The endothelium-lined channels of the body, while parts of an anatomically closed system, with the exception of such structures in the spleen, and possibly the bone marrow, are funtionally open to the diffusion of soluble crystalloid and complex molecular organic substances. This tends to make the blood plasma a nutrient medium for whatever cells it is called on to transport. The blood cells and the endothelium are the normal immediate recipients of its nutrient properties. However, adventitious and nonneoplastic cells of other than hematogenous origin encounter a humoral defense by the body fluids which prevents the development of accessory organs on the basis of cell embolism. Tumor cells are able at times to overcome this natural resistance and to form their characteristic metastatic lesions. It is probable that the number of such secondary foci is very low compared with that of tumor cells which enter the circulation.

The entrance of nonneoplastic tissue cells into the blood and lymph streams is observed but rarely, although, since the pathologist has seen it, the phenomenon must occur considerably more frequently than that. Yet it is doubtful if it is an important way of disposing of surplus or effete cells. In routine microscopic examination of tissues, one occasionally encounters hepatic cells in hepatic veins, renal epithelium in renal veins and acinar cells of the thyroid gland in its blood spaces; and, as will be discussed in more detail subsequently, Sampson showed that endometrial fragments loosened at menstruation find their way not infrequently into the venous sinuses of the uterus. It is easy to inject bone marrow into the periosteal veins of the ribs by the pressure employed in cutting them with a costotome. Since human material is obtained either through surgical operation or at autopsy, it is difficult to draw conclusions taking into accurate account the effect of trauma in the surgical handling of an organ or of postmortem changes in vascular endothelium. The walls of the blood vessels become finely attenuated in the capillary field, and leukocytes, erythrocytes and bone marrow giant cells find their way with ease into the capillaries, as do syncytial cells from the chorionic villi. Hence it seems to me not entirely unwarranted

From the Department of Pathology of Albany Medical College.

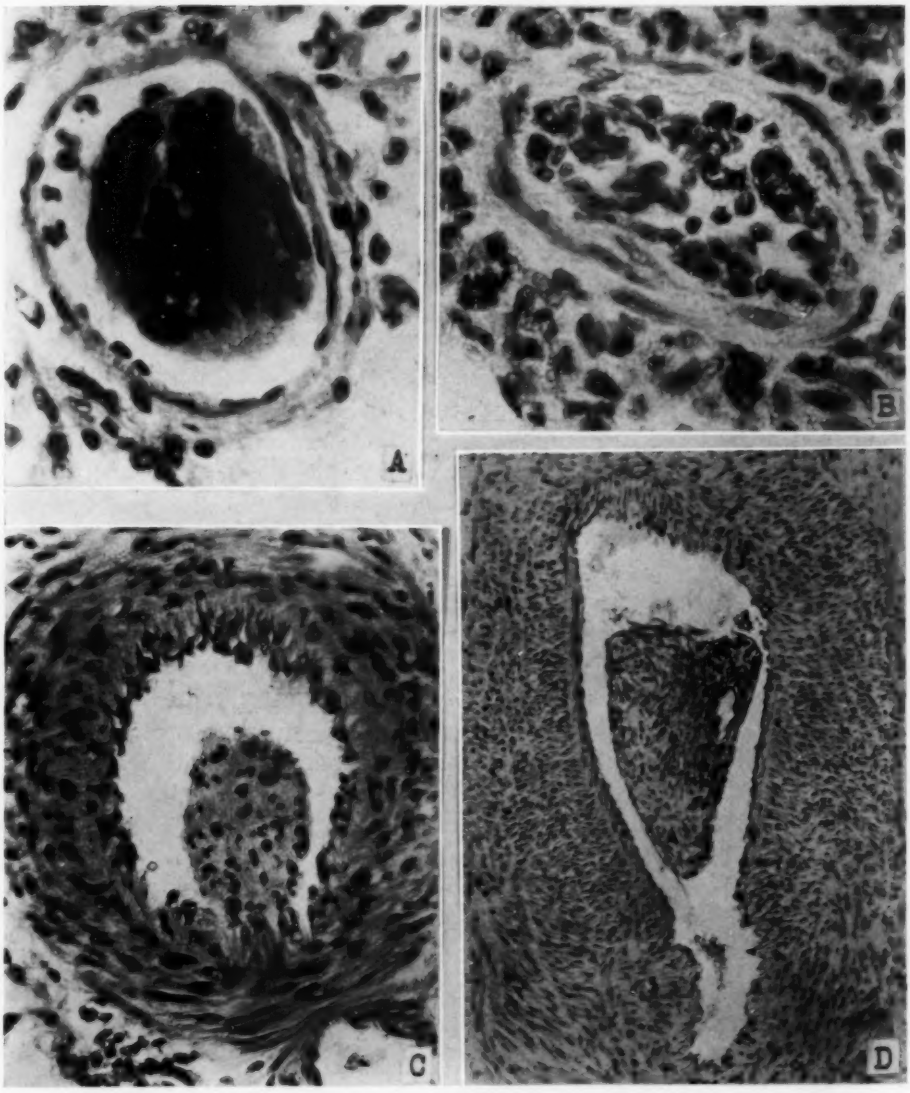
to assume that probably other cells may and do enter the blood and lymph streams in the normal wear and tear of organic activity and are transported to far distant parts, the majority being filtered out in the complex ramifications of the pulmonary bed, with none surviving there or elsewhere. What actually happens to such cells I have endeavored to study experimentally.

TECHNIC

Eleven adult female rabbits from 6 months to 1 year old were used. On each, a laparotomy was performed under aseptic conditions and with ether anesthesia. A horn of the uterus was delivered into the wound, and about 1.5 cm. of its midportion was excised. This piece was opened longitudinally, pinned to a sterile flat piece of cork, and the mucosa gently scraped with a small eye knife. This is the same method that I used in the experimental autotransplantation of endometrial tissue in the rabbit [1] and the monkey.[2] The scrapings were suspended in 3 cc. of rabbit blood serum and this turbid suspension was then injected into the vein of an ear of the same rabbit with a 24 gage hypodermic needle, the time between the actual curettage and the injection, i. e., the maximum time during which the tissue fragments and cells were in the homologous serum, being about 2 minutes. Film preparations of cell suspension obtained in this manner had shown an abundance of cells which were interpreted, purely on morphologic and tinctorial grounds, as being viable at the time of removal or fixation.

Two rabbits died within 30 seconds after the injection of the cell suspension, apparently from the shock of pulmonary embolism, as necropsy revealed nothing else to account for death. The suspension was injected in about 10 seconds. The time for the other injections was lengthened to 1 minute, and no further deaths occurred. It is well known that air can be injected into the rabbit's ear vein in large quantities if given slowly, but a few cubic centimeters injected quickly causes death by air embolism. The other nine rabbits lived with apparently no respiratory or circulatory inconvenience and were killed at intervals of 12 hours, 24 hours, 48 hours, 1 week, 1 month, 69 days, 109 days and 130 days. Three rabbits were in the "resting" stage of the sexual cycle, with small uteri. Four animals were "in heat," with large, hyperemic uteri and hypertrophic endometria, which provided several times as much cellular material in the 1 cm. of horn used as did a similar length of horn from the "resting" animals. Hence the latter did not offer an experiment strictly comparable with that in which the animals used were able to give more abundantly of their hypertrophic membrane, but since the findings in all cases were rather similar, these animals are included in

1. Jacobsen, V. C.: Arch. Surg. **5**:281, 1922.
2. Jacobsen, V. C.: Arch. Path. **1**:169, 1926.



A, a capillary in the lung of a rabbit dying of embolic shock 30 seconds after injection of endometrial suspension. The embolus is composed of many cells of epithelial and stromal types. A few leukocytes have already been attracted to it. *B*, an arteriole in the lung of a rabbit 1 week after injection. Many phagocytes of various types are present, but no cells resembling epithelium. *C*, an arteriole in the lung of a rabbit 109 days after injection. The small thrombus contains polymorphonuclear leukocytes, large mononuclear phagocytes and possibly a few stromal cells of endometrial origin. *D*, a small artery in the lung of a rabbit 130 days after injection. An organized and canalized "thrombus" is seen. Many vessels in this animal's lungs contained similar lesions, which are probably the result of the old endometrial embolism.

the protocol. Two rabbits were pregnant, the gestation period being estimated as about two-thirds complete. The intersegmental endometrium from these animals was used, care being taken not to infringe on the gestation sac. As is invariably the case after this operation, the rabbits aborted within 24 hours. One rabbit (102 days) was a few days postpartum, with lactating mammary glands.

RESULTS

Postmortem examination revealed in no case organic disease of any importance, certainly none referable to the endometrial embolism, except in the lungs of those animals examined within 48 hours after the injection. The two rabbits that died within 30 seconds following the injection showed normal lungs grossly. Microscopically, cells of epithelial appearance were found occluding many arterioles, and a deposit of fibrin was usually seen mingled with the cells. Single cells suggesting epithelium were found in many capillaries of the lungs. No edema, hemorrhage or suggestion of infarction was noted. The heart, spleen, liver and kidneys were normal, and no evidence of cell embolism could be made out.

Two rabbits killed 48 hours and 1 week, respectively, after the operation showed normal organs, except the lungs, which presented numerous punctate red lesions beneath the pleura and scattered throughout the deeper substance. The consistence was scarcely altered, and nothing grossly resembling an infarct was found. Microscopically, each red area consisted of a thrombosed arteriole, the thrombus containing pyknotic nuclei and nuclear fragments, hyaline fibrinous material, proliferated endothelial cells and possibly some stromal cells. A few eosinophilic leukocytes were present just outside the vessels, and the alveolar capillaries were dilated but empty.

After 1 month, and over 4 months, the animals were in good condition, and postmortem examination revealed normal thoracic and abdominal viscera. Microscopically, the liver, kidneys, spleen and heart were normal. In the lungs, the alveolar structure was normal, and only by careful search of many sections could evidence of old embolism be found. At least there were arterioles of medium and precapillary size which were occluded and some partly closed by organized mural thrombi. No epithelial elements could be identified.

COMMENT

The conclusion to be drawn from this work is that in the rabbit parenteral injection of living autologous endometrial epithelium and stromal cells is not likely to result in intravascular growth of endometrial tissue, whether the animal at the time of the operation is pregnant, post-

partum, in "heat" or in the "resting" stage of the sexual cycle. The conditions of the experiment, however, narrow considerably the application of these findings to human cases. A certain degree of mechanical trauma was done in preparing the endometrial cells for injection. The blood serum of a rabbit was certainly the vehicle of choice, although autologous rather than homologous serum would of course have been more compatible with the animal's own cells. It was felt that reducing the time factor was even more important than insisting on the use of autologous serum, since the interval during which the cells were in vitro was usually less than 1 minute at room temperature.

The bulk of the cellular material was undoubtedly filtered out in the lungs. In none of the rabbits was there a suggestion of survival of any of these cells, except possibly some stromal cells, for longer than 1 week. After 1 week no viable cells definitely of embolic origin could be identified. Apparently the capillary field of the lung is not the most fertile soil for the propagation of ectopic tissue. Many single cells must have passed through the lungs into the systemic capillaries, but in such organs as the heart, spleen, kidneys and liver no adventitious cells could be found.

The study is one of a series concerning the very interesting human condition now known broadly as "ectopic endometriosis." In his paper entitled, "Inguinal Endometriosis,"[3] Sampson discussed the veins as avenues for the dissemination of endometrial tissue. He had noted that gelatin containing barium or bismuth, when forced into the cavity of the uterus removed at operation, readily escapes into the uterine veins, if the endometrium had been removed or was not intact. Syncytial cells are often found in the lungs and liver of a woman dying during or shortly after labor. Malignant tumors of the uterus, of course, may metastasize to the lungs. He stated, "A histologic study of the menstruating uterus in which the veins have been injected suggests that occasionally endometrial tissue might escape into the receiving sinuses of the uterine mucosa and remain in the uterine wall or even be carried to the lungs or become lodged in some of the branches of the vaginal plexus of veins and grow there. . . . Some of the misplaced endometrial tissue found in the uterus, vagina and vulva, or even in the groin might have such origin." He believed he was warranted in stating that possibly inguinal endometriosis may be secondary to that in the pelvis and, if so, that it may arise from metastasis through superficial uterine or tubal lymph vessels and veins, and also from endometrial tissue escaping into uterine vessels during menstruation.

In a later contribution entitled, "Metastatic or Embolic Endometriosis Due to the Menstrual Dissemination of Endometrial Tissue

3. Sampson, J. A.: Am. J. Obst. & Gynec. **10**:4, 1925.

into the Venous Circulation,"[4] Sampson showed convincingly that "fragments of endometrial tissue, at times, are disseminated into the venous circulation during menstruation, from the mucosa lining the uterine cavity and also from ectopic endometrial foci." He believes, hence, that "metastatic or embolic endometriosis arises from the implantation of these emboli in nearby veins," and that "endometrial tissue set free by menstruation, therefore, is sometimes not only alive but may actually continue to grow if transferred to situations favorable to its existence."

The female peritoneum, more especially that in the pelvis, offers a very favorable soil for transplanted particles of endometrium, and on this fact Sampson and others explain most instances of ectopic endometriosis in women. Jacobsen,[1] and later Michon, Katz and Szenes, Spirito, Dossena, Dahl-Iversen and others, demonstrated that the peritoneum of the rabbit also is a membrane very favorable to the implantation of autologous endometrial fragments. Jacobsen[2] was able to produce similar growths on the pelvic peritoneum of the monkey (Macacus rhesus).

No ectopic endometrial tissue has been found in the human being outside the peritoneal cavity except in direct continuity with a similar growth on the peritoneum or in the region of the inguinal ligaments. No one so far as I am aware has described such tissue in the lungs. Certainly there appears to be a striking difference between the ease with which endometrium grows on peritoneal mesothelium and the difficulty which it finds in engrafting itself on vascular endothelium, except in rare instances in the wall of the uterus itself. Glands have been found in retroperitoneal pelvic lymph nodes, in both male and female, but in the latter sex have not definitely been proved to be of endometrial origin, since the characteristic stroma was not present nor any evidence of the menstruating function.

SUMMARY

The fate of autologous endometrial tissue introduced into the venous circulation was studied in eleven rabbits in the "resting" stage of the sexual cycle, in "heat," postpartum and also in pregnancy. The operation consisted of laparotomy, with removal of about 1 cm. of a uterine horn, curettage of this portion, suspension of the scrapings in 3 cc. of homologous blood serum at room temperature, and immediate injection into the rabbit's ear vein. Histologic study of the tissues was made 30 seconds, 12 hours, 24 hours, 48 hours, 1 week, 1 month, 69 days, 79 days, 109 days and 130 days, after operation, the animals, except for those which died of "embolic shock" 30 seconds after the injection, remaining in good health during the entire period of their survival. The

4. Sampson, J. A.: Am. J. Path. **3**:93, 1927.

bulk of the cellular material was apparently filtered out in the pulmonary arterioles and capillaries, no adventitious cells being found in the heart, spleen, kidneys or liver. Embolic cells, apparently viable, could be recognized one week after injection, but none could be identified after that time. Stromal cells possibly survive longer than epithelium. Fibrin is deposited about the cell emboli, their cytoplasm gradually disappears, and the nuclei become pyknotic and break up, the embolus becoming converted into a hyaline mass in the smaller vessels and organized in the larger arterioles. Complete absorption or autolysis results in clearing of the pulmonary vessels of the autologous cell masses with no suggestion of formation of new endometrial tissue. These results are in agreement with the distribution of the characteristic lesions in cases of human ectopic endometriosis. While Sampson has found a venous dissemination of endometrial tissue within the human uterus and possibly in the groin, no instance of metastasis of nonneoplastic endometrial emboli has yet been observed above the diaphragm.

FENESTRATED HAMMOCK-LIKE STRUCTURE IN THE LEFT CARDIAC ATRIUM

REVIEW OF THE LITERATURE AND REPORT OF A CASE

FERDINAND C. HELWIG, M.D.
KANSAS CITY, MO.

Anomalous cords and reticula are not rare occurrences in the right cardiac atrium. They have been observed in about 1.5 per cent of all necropsies in my experience.[1] Similar anomalies in the left atrium, however, are apparently unusual. Instances of anomalous cords and reticula and scattered instances of septums and diaphragms in this cardiac chamber have all been recorded, but no one has ever collected the reported instances. After a careful search of the literature, I have not been able to find a structure exactly similar to that which I wish here to report.

REPORT OF CASE

A man, 58 years old, was brought to St. Luke's Hospital, suffering from a severe abdominal injury caused by jumping from a third story window. He died five days later, and a ruptured gallbladder and biliary peritonitis were apparently the cause of death. Examination of his chest, while he was in the hospital, revealed no clinical evidence of any cardiac trouble. The peculiar atrial anomaly to be described was found during the routine necropsy.

The heart weighed 275 Gm.; the valves showed normal measurements (tricuspid, 12 cm.; pulmonic, 7.5 cm.; aortic, 7 cm.; mitral, 10.5 cm.). A low grade sclerosis of the coronary arteries was present, but the heart was otherwise essentially normal except that in the left atrium a thick, endothelium-covered, fenestrated band was found. This band was suspended from three attachments in the roof of the auricle below the openings of the pulmonary veins. It arose from the upper margin of the interauricular wall 2 cm. above the auricular appendage from the upper border of the foramen ovali. One heavy band 3 mm. in diameter was the chief anterior attachment. The band fanned out into a thin transparent membrane to attach along the auricular wall for a distance of about 18 mm. This membrane had four fine fenestrations, measuring about 1 to 2 mm. in diameter, along the posterior insertion in the interauricular septum where it again attached to the wall, thickening up, so to speak, into a heavy, ribbed ligament about 4 mm. in thickness. From these two points of major attachment, anterior and posterior, the band swung across the roof of the auricle. About 10 mm. from the interauricular wall, in the main ribbon, a large oval fenestration 10 by 8 mm. was seen, which showed one fine filiform strand stretching across it, attaching anteriorly and posteriorly close to the medial border of the large fenestration. The lateral insertion in the auricular endocardium was by a band, heavy at both borders and considerably

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From the Department of Pathology, St. Luke's Hospital.

1. Helwig, F. C.: Am. J. Path. **8**:73, 1932.

thinner in the middle. The attachment here measured about 10 mm. in width. The thickness of the lateral borders of the lateral and of the mesial attachments was of about the same character. The entire hammock-like structure appeared to be covered with shiny, smooth endothelium. The hammock was anchored to the medial wall 35 mm. above the insertion of the aortic leaflet of the mitral valve, and laterally about 30 mm. above the attachment of the lateral leaflet of the mitral valve on the lateral wall of the auricle.

A section was removed from the atrial "hammock" just proximal to its insertion in the interatrial septum. The surface of the structure was covered with a flat, single layer of cells which showed only rare nuclei of long, thin, pyknotic character. Immediately beneath this layer there was a dense, more or less homogeneous, hyaline zone of almost anuclear fibrous tissue, and beneath this a looser type of fibrous tissue was seen in which cardiac muscle was present in rather large amounts.

Another section taken through the "hammock" in its middle third showed a picture similar to that seen in the first section, thus illustrating the fact that the structure was abundantly supplied with cardiac muscle throughout.

CASES OF ANOMALOUS CORDS AND RETICULA RECORDED IN THE LITERATURE

In 1927, Kleine [2] reviewed a number of the reported instances of left atrial cords and reticula and added one case of his own. The following is a brief summary of the cases collected by Kleine, the majority of which I have been able to read in the original; hence, a few minor changes have been made in Kleine's descriptions:

Biesiadecki.[3]—The middle of the anterior margin of the valve of the foramen ovale was not adherent to the septum, but extended like a thread along the posterior leaflet of the mitral valve by three thin strands.

Feigl.[4]—This anomaly was almost identical with the one described by Biesiadecki. A tendinous thread was attached adjacent to the valve margin on the posterior valve leaflet.

Przewoski.[5]—A long thread ran obliquely across the left auricular lumen; no further data were obtained.

Rolleston.[6]—A round, fibrous cord crossed over the orifice of the mitral valve. It was attached to the outer wall of the auricle below and behind the appendix and ran downward and to the right, to be attached to the septal wall of the auricle below and in front of the fossa ovalis.

Abbott-Hamilton.[7]—This case was one of an anomalous cord reported by Hamilton in 1899 and was really in the left ventricle, although Kleine incorrectly quoted Abbott from Goforth's article.

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2. Kleine, H. O.: Virchows Arch. f. path. Anat. **267**:281, 1928.
3. Biesiadecki: Virchows Arch. f. path. Anat. **145**:649, 1896; cited by Kleine.[2]
4. Feigl, cited by Kleine.[2]
5. Przewoski, E.: Zentralbl. f. path. Anat. **8**:151, 1897; cited by Kleine.[2]
6. Rolleston, H.: Proceedings of the Anatomical Society of Great Britain and Ireland, February, 1896, in J. Anat. & Physiol. **30**:V, 1896.
7. Hamilton, W. F.: Montreal M. J. **28**:508, 1899.

Hosch.[8]—A tendinous thread 1.5 cm. in diameter, extended from the free border of the posterior mitral leaflet up to the anterior beginning of the septum of the foramen ovale and thence coursed downward to the border of the valve, to become one branch of a forked, tendinous strand.

Aschoff.[9]—A threadlike strand extended from the anterior border of the valve of the foramen ovale to the aortic floor of the mitral valve.

Goforth.[10]—A smooth, threadlike, glistening cord, arising in the wall of the right auricle, pierced obliquely the interauricular septum, then passed down through the mitral valve into the left ventricle, there forming a parabola-like curve. This cord then coursed upward, piercing the anterior cusp of the aortic valve, and attached to the wall of the aorta 8 mm. beyond the valve cusp. The cord was 12 cm. long.

Kleine.[2]—The lower border of the valve of the foramen ovale was drawn out into a free cord the size of a hair-pin which ran downward through the atrial lumen, uniting with the free border of the right-sided contact position of the two mitral leaflet attachments.

In none of the foregoing cases were clinical manifestations mentioned that might have been attributable to these cords except in the cases of Goforth and Kleine. Goforth's patient had an apical cardiac murmur which was described as a "cross between a hum and a friction rub." In Kleine's case, the patient had a "blowing systolic cardiac murmur," but died from streptococcic mitral endocarditis, which may have been the cause of the murmur.

In a further search of the literature, I was able to find nine additional cases that belong to the general class of cords and reticula in the left cardiac atrium:

Sperino.[11]—A cord 5 cm. long extended from the free margin of the base of the mitral valve, traveled up into the auricle and sent out branches to attach to the interauricular septum. It then curved backward somewhat and inserted into the auricular wall as a webbed, falciform ligament.

Hepburn.[12]—The heart, which was obtained from an adult man, was normal except for a deep, anomalous cleft in the left auricular appendage, so that it presented the appearance of two appendages. The inner surface of each portion showed characteristic musculi pectinati. The pulmonary veins from the right lung entered the auricle by two orifices, while those from the left lung inserted in a common trunk to enter the auricle by one orifice. In the cavity of the auricle, there was a distinct moderator band of a thickness resembling whipcord. Its upper end was attached to the auricular wall immediately above and in front of the orifice of the pulmonary vein; the lower end was attached to the interauricular septum between the position of the fossa ovalis and the mitral orifice. The lower end gave off some fine fibrils, of which a few became continuous with the auricular

8. Hosch, P. H.: Frankfurt. Ztschr. f. Path. **1**:563, 1907.
9. Aschoff, L., quoted by Kleine.[2]
10. Goforth, J. L.: J. A. M. A. **86**:1612, 1926.
11. Sperino, quoted by de Vecchi.[13]
12. Hepburn, D.: J. Anat. & Physiol. **30**:582, 1896.

aspect of the base of the anterior cusp or segment of the mitral valve. The removal of the endocardium demonstrated the continuity of this moderator band with the heart substance.

de Vecchi.[13]—A man, 64 years old, died of pneumonia. In the left auricle, a reticular structure was seen which started on the distal edge at the middle of the aortic leaflet of the mitral valve. It traveled on the surface of the mitral valve up to the interauricular septum 19 mm., where it continued for 6 mm. and became lost in the auricular endocardium. It began again above this point, stretching out in a fan-shaped manner, and extended up a further distance of about 3 cm., where it attached to a valvelike excrescence of the interauricular septum, at which point a fissure was found connecting the two auricles.

Sinibaldi.[14]—The patient was a woman of 67 who died of pulmonary tumor and myocardial degeneration. No symptoms were attributable to the network, but in the right auricle a typical Chiari network was found. In the left auricle there was a bandlike structure which extended from the interauricular wall to a point of attachment on the aortic leaflet of the mitral valve. This extended out, parallel with the valve, for a distance of from 7 to 9 mm. in the form of a muscular band. Beneath this band, in the auricular endocardium, a narrow fissure was found. The bandlike structure ended in a fan-shaped manner by attaching to the auricular wall. Five millimeters above the band, another tendinous cord 1 mm. in diameter was seen. This traveled for a distance of about 24 mm. in a more or less parallel direction with the aforementioned band, which lay beneath it. Five millimeters above this cord, and starting from it there was yet another similar cordlike structure 35 mm. long and 3 mm. in diameter which had an appendage projecting from its posterior third which forked into two branches 5 to 6 mm. long. The first of these two branches again bifurcated before insertion into the auricular endocardium, while the latter merely inserted by one strand.

de Vries.[15]—In the left atrium was a tendinous cord that extended from the margin of the foramen ovale over the wall of the left auricle to the posterior leaflet of the mitral valve.

Bolk.[16]—A report of this case was not published, but the anomaly was referred to by de Vries. Bolk observed a tendinous, cordlike structure which attached to the midportion of the valve of the foramen ovale and extended toward the opening of the right pulmonary vein, inserting into the left auricular wall just beneath the venous ostium.

Spring.[17]—A man, 63 years old, died of cerebral hemorrhage. The heart was essentially normal except for a threadlike tendon scarcely 1 mm. in diameter which was found in the left atrium. It was attached close to the anterior margin of the valve of the foramen ovale, from which point it ran free the entire length of the auricular wall of the anterior mitral leaflet where it again attached to the apex of this valve at the point of insertion of the valvular chordae tendineae of the anterior and posterior papillary muscles.

Frizzi.[18]—A woman, 60 years old, died from recurring erysipelas and septicemia. No symptoms or signs referrable to the aberrant cord in the left auricle

13. de Vecchi, B.: Anat. Anz. **20**:374, 1901.
14. Sinibaldi, G.: Anat. Anz. **25**:398, 1904.
15. de Vries, cited by Mönckeberg: Verhandl. d. deutsch. path. Gesellsch. **12**:160, 1908.
16. Bolk, cited by de Vries.[15]
17. Spring, K.: Virchows Arch. f. path. Anat. **252**:263, 1924.
18. Frizzi, L.: Cuore e circolaz. **13**:459, 1929.

were ever elicited clinically. The heart weighed 550 Gm., the valves were dilated, and there were atheromatous ulcers of the aorta. From the free border of the superior margin of the aortic leaflet of the mitral valve a tendinous filament arose and traveled upward in a straight line to the inferior margin of the fossa ovalis, which was patent. The cord measured 3.5 cm. in length, was of cylindric form and had a maximum diameter of 2 mm. in the middle third and of about 1 mm. at the two extremities. About 1 cm. from its upper attachment, it flattened somewhat and expanded in a fanlike manner to insert into the inferior margin of the fossa ovalis.

Costa.[19]—In the course of an article on pulmonary atresia with fenestrations on the fossa ovalis, Costa mentioned an infant 13 months old who died with sarcoma of the suprarenal gland. In the left atrium, a cordlike structure was found arising from the margin of the foramen ovale, which then passed downward, inserting into the auricular surface of the anterior mitral segment.

CASES OF ATRIAL SEPTUMS AND DIAPHRAGMS

In addition to these reticula and cords, septums, diaphragms and so-called "triatrial hearts" have also been recorded, brief reviews of which follow:

Church.[20]—A woman, 38 years old, entered St. Bartholomew's Hospital, London, with a marked dyspnea, generalized anasarca and a rapid, irregular pulse. The edema had been present for several weeks. Her past history was negative except for attacks of hemoptysis with several of her pregnancies. After nine days in the hospital, she died following a sudden acute attack of pain in the chest and with all the symptoms of severe cardiac embarrassment. At necropsy, the lungs were edematous, but all the other viscera were natural except the heart, which weighed 10.5 oz. (284.9 Gm.) and showed no hypertrophy. The left auricle was divided by a membranous septum extending completely across it and separating the portion of the auricle in connection with the septum auricularum and that into which the pulmonary veins open from the auricular appendage and the portion immediately in connection with the auriculoventricular opening. There was an elliptic opening in the upper part of the septum which measured 0.4 in. (1 cm.) transversely and 0.7 in. (1.75 cm.) longitudinally. The general shape of the upper chamber was somewhat like that of a funnel, the neck of the funnel resting on the base of the septum ventriculorum. The atrial wall was not thickened, but the capacity of the two chambers must have greatly exceeded that of a normal auricle. On the exterior of the auricle, a depressed groove marked the line of the septum. The pulmonary veins about the root of the right lung were of unusual size, but no abnormal disposition was noticed.

Fowler.[21]—A man, 42 years old, died from primary cancer of the liver. No history or symptoms referable to the heart were obtained. At necropsy, the heart was found to be enlarged, weighing 13.5 oz. All the valves were competent and normal. In the left auricle there was a membranous band that resembled, in texture, the pulmonary cusps. This band varied in width from ¾ to 1 inch (1.9 to 2.5 cm.). The surfaces were smooth and shiny, and some fine muscular fibers, continuous with those at the auricular wall, could be seen running through its

19. Costa, A.: Clin. med. ital. **61**:566, 1930.

20. Church, W. S.: Tr. Path. Soc. London **19**:188, 1868.

21. Fowler, J. K.: Tr. Path. Soc. London **33**:77, 1882.

substance. It was attached internally to the wall of the auricle above and to the side of the annulus ovalis, and was continuous with the membrane covering the foramen ovale. The band also had attachments to the inner wall of the auricle by thin bands and fine filaments. The former were perforated in several places, giving the band a reticular appearance at this part. With the heart in position, the thin edges of the membrane were nearly vertical. In crossing to the opposite wall of the auricle, the membrane was slightly twisted, and became blended with the endocardium just beyond the opening of the auricular appendix and between the points of entrance of the inferior pulmonary veins. A thin filament given off from its lower edges joined the wall about ½ inch (1.3 cm.) below. The foramen ovale presented a valvelike opening at its inner edge about ¼ inch (0.61 cm.) in length. The auricle was of normal size.

Preisz.[22]—In an 11 year old girl, on the anterior wall of the cardiac auricle, corresponding to the anterior side of the auricular septum, a fleshy ridge was found; to the left and behind this ridge, three pulmonary veins were found to open. To the right of this, one upper systemic vein was also found. Opposite this ridge, the opening of the lower systemic vein was encountered, and there was no trace of a valvular apparatus at its opening. The lateral part of the left auricular half, with the left auricular appendage, was separated from the remainder of the auricular space by a septum lying close to the left margin of the left pulmonic vein. This part of the auricle had no vessels, and it was connected with the left ventricle through the left venous ostium.

Preisz.[22]—In a 3 year old boy the heart was found to be transposed. The right ventricle was very large, and the left was quite small. The aorta was large and the pulmonary artery very small, and both of these vessels extended from the left upper portion of the right ventricle. The rudimentary left ventricle, on the other hand, had no direct outlet. The left auricle was divided into two chambers, one right and one left. The latter was quite small and included little more than the auricular appendage, and there were no vessels leading from it. The right chamber was considerably larger than the left. The septum that divided these two parts of the auricle extended forward from the posterior atrial wall, bent somewhat toward the midline, and did not extend clear across to the anterior wall, but ended in a concave border, thus forming a canal connecting the two chambers of the left atrium.

Griffith.[23]—The left cardiac auricle was divided by a fibromuscular septum into two halves; the upper half received the pulmonary veins, and the lower chamber communicated with the auricular appendage and the left ventricle. The band, which was about as thick as note paper, was mainly fibrous, but presented muscle fibers scattered chiefly on its upper or posterior aspect, continuous to the left with those of the auricular wall and to the right with muscular fibers that were spread over the valve of the foramen ovale. In its anterior margin, there was a small calcareous spicule.

Martin.[24]—The only description of this case was a notation in the Proceedings of the Anatomical Society of Great Britain and Ireland where it was recorded that "Professor Martin showed a heart in which the left auricle was divided by a horizontal septum into a superior and an inferior compartment."

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22. Preisz, H.: Beitr. z. path. Anat. u. z. allg. Path. **7**:272, 1889.

23. Griffith, T. W.: J. Anat. & Physiol. **30**:6, 1896.

24. Martin, Sidney: Proceedings of the Anatomical Society of Great Britain and Ireland, July, 1899, J. Anat. & Physiol. **33**:xxxi, 1899.

Griffith.[25]—Griffith observed a similar case in a man, 48 years old, who died from Bright's disease. The left auricle of the hypertrophied heart was partly divided into two halves by a fibrous band forming an upper and a lower chamber in the left auricle. The band originated from the auricular septum. An opening admitting two fingers was present, through which the two chambers communicated; numerous other smaller openings were also present. The pulmonary veins emptied into the upper half. The foramen ovale was completely closed.

Potter and Ranson.[26]—A child died of asphyxia. The body was well formed and to all appearances was normal. The heart showed no degenerative changes and was normal in every way except for the presence of a septum across the left auricle which divided the auricle into a posterior superior chamber receiving the

Photograph of the heart showing the left auricle and ventricle opened. In the roof of the left atrium, a fenestrated, hammock-like structure can be seen swinging across the auricle.

five pulmonary veins, and a left antero-inferior chamber connecting with the auricular appendage and the left ventricle.

Borst.[27]—A woman, 38 years old, had been dyspneic since childhood. On examination, she had a presystolic murmur at the apex and some increase in cardiac dulness. At necropsy, the heart revealed that the lumen of the left auricle was divided into two distinct halves by a diaphragm. The diaphragm thus formed an upper and a lower chamber. Into the former, which was the larger of the two,

25. Griffith, T. W.: J. Anat. & Physiol. **37**:255, 1903.
26. Potter, Peter, and Ranson, S. W.: J. Anat. & Physiol. **39**:69, 1904.
27. Borst, M.: Verhandl. d. deutsch. path. Gesellsch. **9**:178, 1905.

five pulmonary veins entered, while the lower chamber communicated with the mitral valve and the auricular appendage. The diaphragm coursed obliquely through the entire auricle, extending from above anteriorly and exteriorly downward, posteriorly and medially. Its point of insertion corresponded anteriorly and laterally to the borders between the upper and anterior or lateral wall of the entire auricle. Medially, it inserted into the septum of the right and left auricle, corresponding to the lower margin of the fossa ovalis (3 mm. above this margin). Posteriorly, the diaphragm was inserted 1.5 cm. above the insertion of the posterior leaflet of the mitral valve. At the latter point, there was a defect in the diaphragm. Between the free margin and the posterior wall of the auricle, there was a round opening 1 cm. in diameter, which was the only point of communication between the two left auricular chambers. The border of this hole was thickened. The diaphragm was covered by endocardium and contained bundles of cardiac muscle. At the point of insertion, there was a small calcareous plate 2 mm. in diameter embedded in the tissue of the diaphragm. The valvula of the foramen ovale was absent, and the closure of the valve was achieved by coarse muscle striae.

Hosch.[8]—A child, 25 days old, entered the hospital because of conjunctivitis. On physical examination, the infant was cyanotic, crepitant râles were present in both lungs, and a systolic blowing murmur was heard. At necropsy, a patent foramen ovale and ductus botalli were found. There was endarteritis of the right common carotid, and in the left auricle a transverse diaphragm from 0.25 to 0.5 mm. thick was found. This septum bulged downward in the form of an irregular, uneven funnel. Medially, it formed a continuation of the valvula foraminis ovalis. The patent foramen ovale led into the lower portion of the left auricle, which was in communication with the auricular appendage. Posterior to the foramen ovale, there was a small opening which led to the right auricle. The septum itself contained a number of various-sized openings, many of which led to a space limited above and below by a septum, the latter being double in this region. Into the upper portion of the left auricle, three pulmonary veins emptied, a large one on the left and two smaller ones on the right.

Stoeber.[28]—A child who died shortly after birth revealed at necropsy a septum in the left cardiac auricle, and there was no opening in it. The veins of both pulmonary lobes emptied into the right auricle, so that the upper and smaller portion of the left auricle received only the veins of both lower lobes. The middle lobe of the right lung was absent. The foramen ovale was patent. There was a rudimentary valvula foraminis ovalis represented by a membranous structure that passed directly into the auricular septum.

Thilo.[29]—In this case, a bandlike structure was found in the left cardiac atrium. One half of the band arose from the valve of the foramen ovale and the other half from the interauricular septum. The structure inserted into the endocardium on the inferior border of the ostium of the left pulmonary vein. No further data were obtainable.

William and Abrikossoff.[30]—A necropsy was performed on the body of an 11 year old boy who clinically had shown edema, ascites, an enlarged liver and an enlarged heart with a systolic murmur and a precardial friction rub. The heart was dilated and hypertrophied. The left auricle was widely dilated, and its cavity was divided into two portions, an upper and a lower, by a transverse septum that

28. Stoeber, H.: Virchows Arch. f. path. Anat. **193**:252, 1908.

29. Thilo, J. D., cited by Spring[17] and Hosch.[8]

30. William, N., and Abrikossoff, A.: Virchows Arch. f. path. Anat. **203**:406, 1911.

passed directly into the wall of the auricle at its margins. In the anteromedial angle of the septum, there was an opening 0.5 cm. in diameter through which the upper and lower cavities of the auricle communicated. The septum was made up of muscle and connective tissue.

Patten and Taggert.[31]—A white girl 3 months old had been dyspneic and cyanotic since birth. A tick-tock-like sound was heard on auscultation of the heart. An x-ray picture showed the heart to be globular. At necropsy, on external inspection, the heart showed a median bulging of the atrial region, marked off on either side by fairly definite lines of depression. This dilatation was found to be an accessory median atrial chamber which was wedge-shaped with its bulging base presenting on the dorsocaudal wall of the atrium and the apex of the wedge directed ventrocephalically. Both left pulmonary veins opened by a common funnel into the median chamber as did the group of three right inferior pulmonary veins.

COMMENT

Various explanations are given to account for these peculiar left atrial structures, and theories similar to those used for like structures in the right atrium have been advanced to account for their origin. Przewoski [5] suggested that the aberrant chordae mentioned in the first group of cases recorded in this review may arise from atrophied muscle bundles in the trabeculae of the left atrium. Chiari [32] believed that these cords and diaphragms might be caused by a separation of the primary and secondary septums, thus producing a partial division of the left atrium; while Hosch [8] thought that a congenital anomaly of the septum primum could account for the formation of some of the structures. Aschoff [9] and de Vries [15] agreed with Hosch. Kleine,[2] in a long discussion of his case, suggested that those instances in which only chordae were present might be accounted for on the basis of remains of an earlier endocarditis. He also thought, however, that a defective development of the primary septum could cause these anomalies. Borst,[27] in discussing his case of "triatrial" heart, found the pulmonary veins in the heart that he described to be defectively placed, and he explained the division of the left auricle as being due to mechanical pressure pushing aside the primary septum, with the formation of a left auricular diaphragm.

It will be noted that the majority of the writers favor the theory of maldevelopment of the septum primum to account for the atrial anomalies under discussion, and this seems to be a very logical conclusion, particularly in those cases in which bands and septums were found stretching across the atrium. The displacement of the primary septum to the left appears to be the most reasonable explanation of the mechanism involved.

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31. Patten, B. M., and Taggert, W. B.: Arch. Path. **8**:894, 1929.

32. Chiari, quoted by Kleine, H. O.: Verhandl. d. deutsch. path. Gesellsch. **9**:192, 1905.

In the case which I have recorded there was present a marked irregularity in the area where the septum primum and secundum had joined; there was a semiflattened band in the form of a loop attached above and below on the upper and lateral rim of the closed foramen ovale. Moreover, it appeared grossly that the "hammock-like" band which tended to divide the left auricle into upper and lower portions might represent a further maldevelopment in the formation of the primary septum. Although the band was attached at both ends, it was not attached on either side, which leaves the explanation for the exact origin of its peculiar formation obscure. However, a point of importance was observed in the histologic sections of the "hammock" which revealed an abundant supply of cardiac muscle under the endocardium, which fact tends to strengthen the hypothesis that the maldevelopment was of an embryonal nature and was probably due to some imperfection in the development of the septum primum.

Photographs of this structure were submitted to Professor Jordan of the Department of Embryology of the University of Virginia. He was unwilling to do more than state that the structure was probably the result of faulty development of the auricular endocardium.

SUMMARY

A hammock-like, fenestrated band suspended in the roof of the left cardiac atrium is described. An exactly similar structure could not be found described in the literature. This structure was probably produced by some developmental irregularity of the septum primum in embryonal life. In reviewing the literature of similar anomalies, seventeen instances of reticula and cords and fourteen cases of septums and diaphragms were found reported, and these cases are here briefly summarized. These anomalies are of little clinical importance except in those instances in which they impede the free passage of the blood. In some cases, definite clinical signs attributable to the anomaly were present, but in most cases, as in the unusual case reported here, no clinical indication of the condition was observed.

BONE LESIONS IN RATS PRODUCED BY THE SUBSTITUTION OF BERYLLIUM FOR CALCIUM IN THE DIET

SHELDON A. JACOBSON, M.D.
Brown Research Fellow
NEW YORK

Some of the alkaline metals have aroused considerable interest by virtue of their action in predisposing experimental animals to rickets. Branion, Guyatt and Kay [1] proved that replacement of the calcium of the Steenbock diet 2965 with beryllium results in the radiographic and histologic picture of rickets, despite a generous allowance of cod liver oil. It has seemed to me worth while to pursue these studies further.

PROCEDURE

White rats of the Wistar Institute strain were the experimental animals in all of the procedures to be described. They were kept in cages, from two to four rats in each cage, and allowed to eat of their diets ad libitum from a common dish. The amount consumed was not recorded. All animals, except as noted later, received 3 drops of cod liver oil per day each, administered directly into the mouth with a pipet. With the exception, again, of some that will be more particularly referred to, all were kept in a room which, while light, may be considered as having very few ultraviolet rays by virtue of the fact that the experiments were conducted between November and January, and that the windows, facing to the east, were kept almost continuously closed by a thick pane of translucent glass.

FIRST SERIES OF EXPERIMENTS

Group 1.—The Steenbock diet 2965 was fed to six rats in an absolutely dark room. Their weights at the beginning of the experiment varied from 32 to 49 Gm. Cod liver oil was not administered. The animals ate poorly, making slight early gains in weight, which were partly lost again toward the end of the experiment. Rats were put to death at intervals up to thirty-three days. In all that had passed the two week period on the diet there were increasing beading of the ribs and Harrison's groove. Marked cervical lordosis was noted in one at the expiration of the thirty-third day. Histologically, a typical rachitic lesion was found; this has been so often and so well described that it is not considered worth while to present its details in this publication. From this experiment, I feel that the rachitogenic property of the diet in my hands has been demonstrated.

Group 2.—Five small (from 40 to 63 Gm.) and three large (from 72 to 106 Gm.) rats were put on the Steenbock diet 2965. On this regimen they grew,

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From the laboratory of the Hospital for Joint Diseases.

1. Branion, H. D.; Guyatt, B. L., and Kay, H. D.: J. Biol. Chem. **92**:xi, 1931.

although with less than normal rapidity. Grossly, their skeletons were well shaped and hard. On microscopic examination, the bones differed from normal only in the slightly greater reticularity of their osteoid columns at the growth epiphyses. The epiphyseal plates themselves were normally thin; the osteoid trabeculae were actively growing and rapidly calcifying. The cortices were fairly dense, the spongiosa well developed in both shaft and epiphysis. Bone resorption was not a

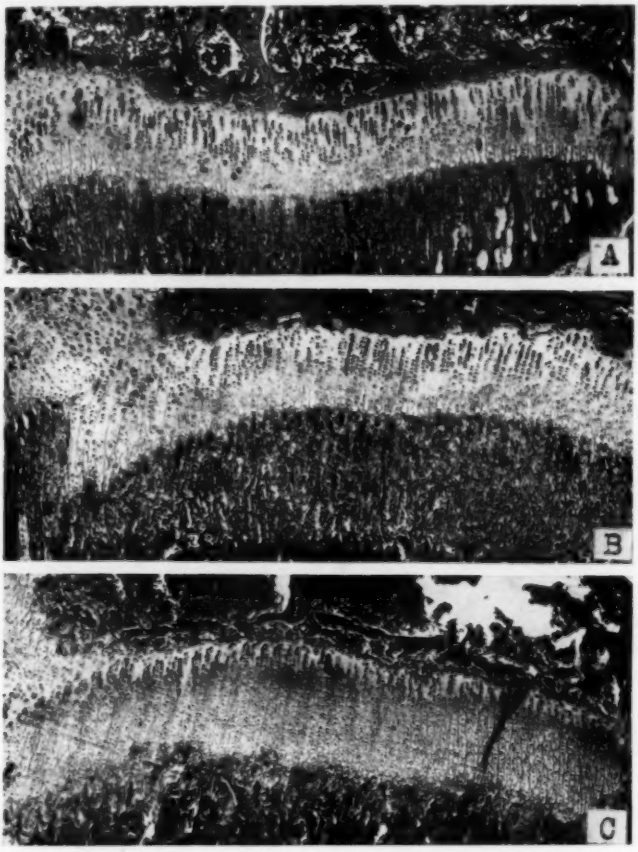

Fig. 1.—*A*, tibia of normal controls; × 25; stained with hematoxylin and eosin. Note the thickness of the proliferative zone of the cartilage plate, the number and thickness of the epiphyseal trabeculae, the straight line of demarcation between the cartilage and bone, and the texture and arrangement of the newly formed trabeculae of the metaphysis.

B, tibia of an animal that was fed the calcium-free Steenbock diet; × 25; stained with hematoxylin and eosin. Note the similarity of the architecture to that of *A*.

C, tibia of an animal on the Steenbock diet plus beryllium; × 25; stained with hematoxylin and eosin. Note the marked thickening of the proliferative zone of the cartilage plate, the irregularity of the demarcation between the line of cartilage and bone, the penetration of marrow into the cartilage, the thinness of the epiphyseal trabeculae and the irregularity of the newly formed trabeculae of the metaphysis.

prominent feature of the picture, osteoclasts being rare. The cartilage showed no abnormality. The marrow was lymphoid. This group constitutes the normal control (fig. 1 *A*).

GROUP 3.—Three rats weighing 40, 42 and 70 Gm., respectively, were put on the Steenbock diet modified only to exclude calcium carbonate. These animals likewise grew at a moderate rate. They were put to death at the twenty-third, thirtieth and forty-second days, respectively. They were fairly well nourished, the bones of the one first killed firm, those of the longest survivor soft. No abnormalities as regards shape of skeleton were noted. This regimen resulted in the development of simple osteoporosis but not of rickets.

The results of histologic examination of the tibia of the rat that was forty-two days on the experimental diet, growing from 72 to 146 Gm., are given. The epiphyseal cartilage plate was of normal thickness. The line of demarcation between it and the growing bone was straight and regular. The osteoid columns were somewhat more reticular than normal, but were fairly straight and orderly in their architecture. Not only here, but elsewhere on the surfaces of cortex and of trabeculae, one saw the pink stain characteristic of osteoid tissue. The trabeculae were decreasing in number; the cortex gave marked evidence of resorption, although osteoclasts were few. There had been periosteal irritation, as evidenced by the appearance of a thick layer of subperiosteal fiber bone (fig. 1 *B*). A rib had a somewhat similar appearance.

GROUP 4.—Fifteen rats varying in weight from 39 to 134 Gm. were put on the Steenbock diet modified by the substitution of a chemically equivalent quantity of beryllium carbonate for calcium carbonate. This diet was evidently unpalatable, as the rats would eat but little or none of it. Not one of them gained weight in the course of the experiment. Of the animals under 60 Gm. in weight, all but one died within thirteen days at the most. One animal was killed on the eighteenth day, after its weight had fallen from 48 to 36 Gm. The larger animals showed losses of as much as 50 per cent within one month. Some of them died and some were killed, the longest experiment lasting thirty-five days. Except for the usual signs of malnutrition and for a constant priapism, no changes were observed in the tissues beyond those affecting the skeleton. The bones, however, were very soft and brittle. On this diet, a lesion closely resembling rickets appeared in young rats of weights usually susceptible to rickets, as described in the following paragraph. Rats over 100 Gm. in weight were refractory to beryllium rickets.

The results of histologic examination of the tibia of a rat which died after a decline in weight from 48 to 33 Gm. in thirteen days are given. The proliferative zone of the epiphyseal cartilage plate was widened to at least four times the normal thickness (less at the edges). The line of demarcation between this and the growing bone was irregular and marked by numerous marrow spaces containing blood elements that pressed their way in among the cartilage cells for short distances. The trabeculae were fairly thick and frequent; they showed, however, as did the cortex to a lesser extent, deposition of osteoid tissue. The marrow was markedly congested. Resorption of the cortex was taking place. Giant cell osteoclasts, however, were not in evidence. There was some slight periosteal bone production. The cortex was fairly thick. The articular cartilage was apparently normal (fig. 1 *C*). A rib showed a very similar picture.

A rat which was thirty days on the diet, and the weight of which fell from 113 to 53 Gm., showed no marked anatomic abnormalities except for some smooth resorption and for marked congestion of the bone marrow. In other words, there was only mild osteoporosis.

SECOND SERIES OF EXPERIMENTS

GROUP 1.—Four young rats varying in weight from 33 to 40 Gm. were kept in a dark room and permitted to eat ad libitum of a diet consisting of chopped horse meat (containing much suet) with 5 per cent tomato juice and butter ad libitum administered every tenth day. No cod liver oil was administered. Animals were killed at intervals up to five weeks. The effect of this diet was seen in osteoporosis, with slight tendency to rickets.

The results of histologic examination of a rat which was twenty-eight days on the diet, and the weight of which rose from 32 to 80 Gm., are given. The humerus showed a cartilaginous epiphyseal plate that was almost completely normal in appearance. It was remarkable only for some irregularity of the cartilage-bone demarcation and for some tendency on the part of the marrow to press in among the cartilage cells. The osteoid trabeculae were few and irregular in contour and arrangement. There was extremely pronounced resorption of the cortex and of trabeculae, in which process giant cell osteoclasts were playing a not too prominent rôle. The marrow was lymphoid. The articular cartilage was not abnormal. The osteoid tissue was practically limited to physiologic areas.

Fig. 2.—Rib of an animal on a meat (calcium-poor) diet; × 50; stained with hematoxylin and eosin. Note the thickness of the proliferative zone of the cartilage plate, the regularity of the line of demarcation between the cartilage and bone, the fewness of the trabeculae and the thinness of the cortex.

GROUP 2.—One rat weighing 42 Gm. was kept for thirteen days and one weighing 48 Gm. for forty-two days on a diet consisting of meat with 2 per cent cod liver oil and 5 per cent tomato juice. At the expirations of these periods the animals were killed. Under these conditions, marked osteoporosis, but not rickets, resulted.

The results of histologic examination of the rib of a rat which increased in weight from 48 to 105 Gm. in forty-two days are given. The cartilaginous epiphyseal plate was completely normal; its demarcation from the growing bone, sharp and regular. The young osteoid trabeculae were slightly more reticular than was normal. The shaft and trabeculae were composed, for the greater part, of poorly calcified tissue. The trabeculae were few and thin. The cortex was likewise extremely thin; there was some periosteal bone formation. Resorption of the cortex was quite active, although giant cells were apparently not responsible for this appearance. The marrow was lymphoid. The articular cartilage was not abnormal (fig. 2).

GROUP 3.—Four rats were kept on a meat diet similar to the diet of group 2 except for the addition of beryllium carbonate in a quantity equivalent to 1.5 per cent calcium carbonate calculated on the basis of the weight of the dry meat, which is assumed to be 25 per cent of the weight of wet meat. The animals ranged in weight from 44 to 68 Gm. All gained rapidly. They were put to death at intervals up to forty-two days. The peak of the gain was reached at the expiration of the fourth week. A rachetoid lesion developed on this regimen.

The results of histologic examination of a 44 Gm. rat which, kept on the diet for thirteen days, gained 27 Gm., are given. The proliferative zone of cartilage cells in the epiphyseal plate was thickened to from two to three times the normal. The line of demarcation between it and the zone of bony growth was fairly regular, although the marrow showed a slight tendency to invade the cartilage. The osteoid trabeculae were fairly straight. There was a thin zone of osteoid deposition on some areas of cortex and of trabeculae, which were fairly numerous. The cortex showed marked thinning and resorption, and giant cell osteoclasts were very numerous and active. The marrow was lymphoid; the articular cartilage was not abnormal. There were some indications of periosteal activity (fig. 3*A*). A section of a rib showed similar changes. The irregularity of the young osteoid columns was somewhat more marked.

The changes described reached their maximum within three weeks, and were no more marked, possibly less so, in the animals killed at the end of the sixth week.

The results of examination of a 47 Gm. rat which, twenty-three days on the diet, gained 43 Gm. in weight, are given. The animal was well nourished, with a moderate amount of fat. Its bones were soft. Histologic examination of a tibia showed that the proliferative zone of the cartilaginous epiphyseal plate was enormously thickened. The line of demarcation separating it from the bone was for the most part not extremely irregular, although there were a few areas in which the marrow pressed very actively in among the cartilage cells. The osteoid trabeculae were decidedly irregular and reticular. There were thick osteoid depositions on cortex and trabeculae. The cortex showed extremely marked resorptive changes in which giant cell osteoclasts played a very prominent rôle. There was some periosteal activity. The marrow was lymphoid. The articular cartilage was apparently normal. A rib showed a similar lesion except for marked irregularity of the demarcation line between the cartilage and bone.

GROUP 4.—Four animals, ranging in weight from 54 to 76 Gm., were put on a diet similar to that given group 3, except that it contained twice the amount of beryllium. They also were killed at approximately ten day intervals. The results were qualitatively similar to those of the preceding group, although the rachetoid

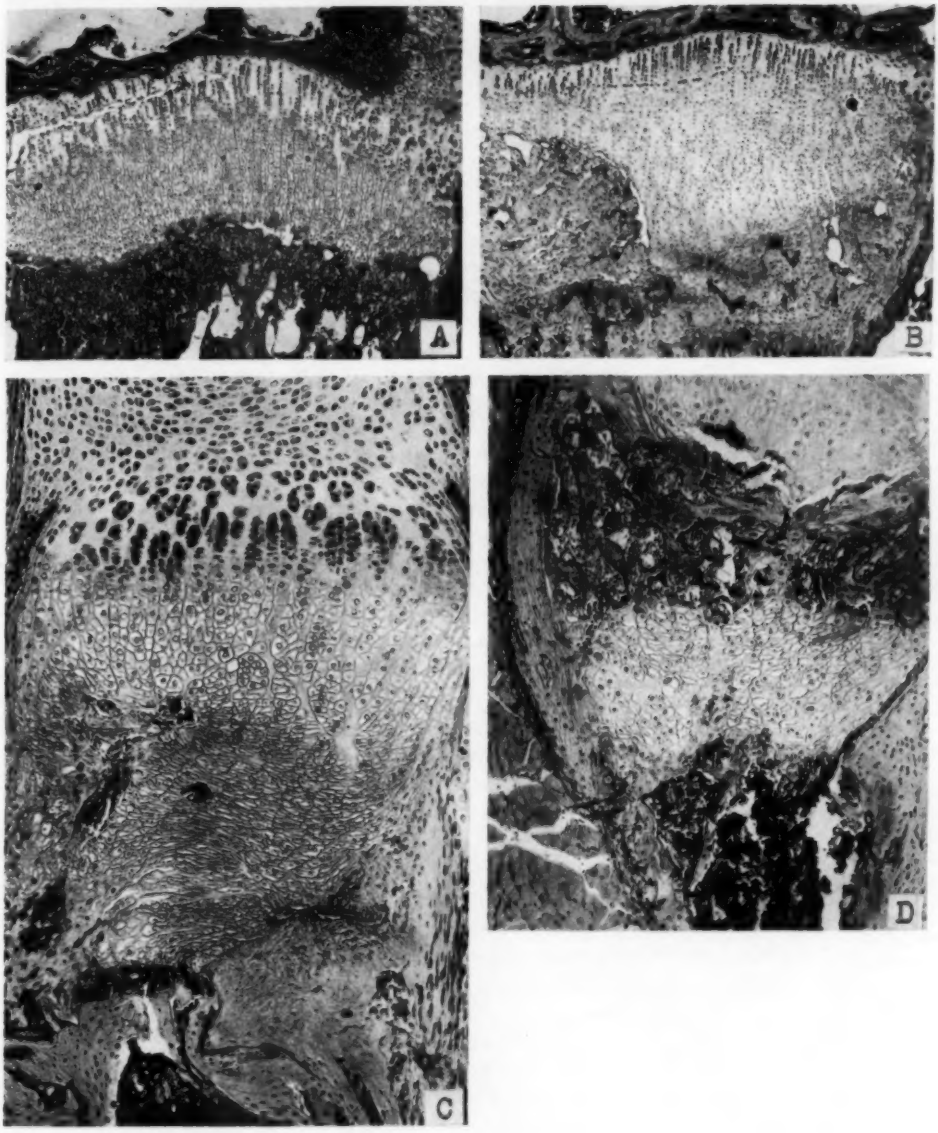

Fig. 3.—*A*, tibia of an animal on a meat and beryllium (1.5 per cent) diet; × 35; stained with hematoxylin and eosin. Note the thickness of the proliferative zone of the cartilage plate, the fewness of the epiphyseal trabeculae, the irregularity of the line of demarcation between the cartilage and bone and the irregularity of the architecture of the newly formed trabeculae of the metaphysis.

B, tibia of an animal that was fed a meat and beryllium (3 per cent) diet; × 35; stained with hematoxylin and eosin. Note the uneven thickening of the proliferative zone of the cartilage plate, the thinness of the epiphyseal trabeculae, with osteoid deposits thereon, the penetration of marrow into the cartilage and the complete loss of the architecture of the metaphysis.

C, rib of the same animal from which tibia in *B* is shown; × 105; stained with hematoxylin and eosin. Note the tremendous thickening and irregularity of the cartilage plate, with penetration of marrow into it, and the complete loss of the architecture of the metaphysis, which is composed almost entirely of osteoid tissue.

D, rib of another animal on the same diet; × 75; stained with hematoxylin and eosin. Note the growth of osteoid along the border of the proliferative zone of the cartilage plate and the ingrowth above the latter, cutting most of the plate off from the costal cartilage.

lesion was somewhat more marked. The results of examination of a 60 Gm. rat which, forty-two days on the diet, gained 14 Gm. in the first nine days, weighing 70 Gm. at the expiration of the experiment, are given. The animal was in fairly good condition; its bones, however, were very soft. The ribs were beaded. Histologic examination of a tibia showed a proliferative zone of the epiphyseal plate which was enormously widened for about one third of its width, but which showed only slight widening for the remaining two thirds. The line of demarcation between this and the growing bone was extremely irregular, so much so, indeed, that it could not at every point be said with certainty what was to be considered cartilage with osteoid and marrow inclusions, and what bone with cartilage inclusions. The young osteoid trabeculae were no longer entitled to be called such, having become shapeless and completely irregular masses of osteoid, separated by rather narrow spaces containing somewhat fibrotic marrow. The cortex, as well as the trabeculae, which were not extremely numerous, was covered by very thick osteoid deposits, which in places had usurped positions in the interior of the cortex, lining haversian canals. There was some evidence of periosteal activity. Some cortical resorption was in progress near the epiphysis. Giant cells, however, did not play a leading rôle. The marrow was lymphoid with a very considerable fatty admixture. The articular cartilage was apparently normal (fig. 3 *B*).

Section of a rib gave an even more chaotic picture as regards the thickened proliferative zone of cartilage and the irregularity of the demarcation between this and what had become broad, almost unbroken, masses of osteoid tissue. The walls of the shaft were thick but apparently poorly calcified. There was a tendency for the process of ossification to extend much further at the circumference of the bone than in its middle (fig. 3 *C*).

A 76 Gm. rat which was on the diet for twenty-three days, with a gain of 42 Gm., is here mentioned because of the extreme irregularity of the zone of ossification which the rib displayed. The advancing osteoid tissue at the circumference of the bone had widened after penetrating deeply into the proliferative zone of the cartilage, coming to occupy the complete diameter of the rib, so that proceeding laterally from the costal cartilage one saw a proliferative zone of cartilage at least three times the normal width; then a zone of osteoid tissue, with marrow spaces, of approximately the same thickness; then a second proliferative zone of cartilage, still of the same thickness, with narrow borders of osteoid tissue at the periphery, and finally, the distorted osteoid columns and the marrow cavity proper. The shaft was thick and calcium-poor; the marrow, lymphoid (fig. 2 *D*).

SUMMARY

The results obtained on group 1 in the first series of experiments demonstrated the rachitogenic properties of the Steenbock diet, while those on group 2 testified to the completeness of the protection afforded by the dosage of cod liver oil used. Group 3 on a calcium-free Steenbock diet emphasized the latter point, since a gross and histologic study of the skeletal material demonstrated that even the very marked osteoporosis brought about by a diet practically calcium-free was completely ineffective in inducing rachetoid lesions.

On the substitution of beryllium, however, for the calcium of the Steenbock diet, a completely different picture in the economy of the

younger rats resulted—this despite the extreme toxicity of the diet as proved by the fact that the animals were able to live on this regimen for periods varying from four to an absolute maximum in one case of eighteen days. As early as the end of the first week definite evidence of rickets appeared, viz., slight piling up of the cells in the proliferative zone of the cartilage plate, with irregularity of the line of demarcation between them and the osteoid trabeculae. A few days later there was a considerable advance in the degree of this lesion, the eight day and the thirteen day animals showing well advanced pathologic changes. This is the more remarkable, in that not only were these animals not actively growing, but they were in fact losing weight rapidly (owing apparently to their not eating the unpalatable beryllium diet), to the extent in each one that survived a week or longer of approximately 33 per cent.

A rat weighing 86 Gm., which died after having lost 21 Gm. on this diet in the course of fifteen days, showed some very early and doubtful rachetoid lesions. Those weighing more than 100 Gm., which lost 50 per cent of their weight before dying or being killed at the end of from three to five weeks showed, as was to be expected, marked osteoporosis but no clearcut signs of rickets. There was considerable irregularity of the line of demarcation between cartilage and bone, with invasion of the cartilage by marrow and extensive osteoid deposition. Thickening of the proliferative zone, however, was not manifest. The rate of growth of these animals was apparently too low for even the powerful rachitogenic action of beryllium to become evident.

An even severer test of the rachitogenic properties of beryllium was furnished by the second series of experiments. These animals, on a diet rich in suet, even when deprived of cod liver oil showed a very considerable resistance to rickets. With the oil, and without any adventitious metal, there was not the faintest sign of any specific pathologic change, the animals being characterized merely by a most extreme type of osteoporosis. Their rate of growth on these diets was truly remarkable. Animals weighing from 42 to 48 Gm. would double their weights within two weeks.

With both the lower (1.5 per cent) and the higher (3 per cent) concentrations of beryllium in the diets, the response was marked. It cannot be said, however, that the severity of the rachetoid lesion produced was a function of the amount of beryllium in the diet. There was a definite relationship to the duration of administration, however, the maximum being attained in about three weeks, the lesion showing no tendency to further progression in twice that length of time. A histologic examination of the material leads one, indeed, to the opinion

that a maximum had been attained. The very bizarre architecture of the metaphysis is sufficiently evident in the illustrations.

As to the mechanism by means of which this disease so closely paralleling rickets is produced, I have no theory to propose. Work is being continued along these lines in the hope of its shedding some light on the nature of rickets.

CONCLUSIONS

A calcium-free Steenbock diet with the addition of cod liver oil brings about osteoporosis but not rickets in young rats.

A calcium-free Steenbock diet with the addition of cod liver oil and beryllium carbonate produces a disease anatomically indistinguishable from rickets.

Rapid loss of weight in the experimental animals does not prevent the development of a marked rachetoid lesion.

A diet consisting of fatty meat with cod liver oil results in extreme osteoporosis but not in rickets.

The addition of 1.5 to 3 per cent beryllium carbonate to such a diet results in a typical rachetoid lesion.

HISTOLOGIC CHANGES IN RABBITS AND IN DOGS FOLLOWING THE INTRAVENOUS INJECTION OF THORIUM PREPARATIONS

EVAN SHUTE, M.D.
AND
M. EDWARD DAVIS, M.D.
CHICAGO

Since the first papers of Bluhbaum, Frik and Kalkbrenner,[1] Radt [2] and Oka [3] there has been widespread interest in the use of colloidal suspensions of thorium for the roentgenologic visualization of viscera. The first preparations used were called tordiol and umbrathor. More recently, thorotrast, which is a less toxic substance, has been introduced. To date, these preparations have been used to visualize the liver, spleen, bone marrow, bowel, ureters, bladder, bronchi and lymph nodes. There has been an increasing tendency to use them in cases of malignant growth, in which they could do little if any harm.

Bluhbaum, Frik and Kalkbrenner [1] used their preparation in patients and dogs. They found no changes in the five dogs used, except a transient anuria in two. There were no undesirable reactions in their patients. Oka [3] found no changes in his dogs, carefully observed over many months, except brief decreases in hemoglobin, red cells and platelets, with slight leukocytosis. He noted only trivial danger signals (fever, chills and diarrhea) in six patients in whom he used tordiol.

Von Adler-Racz [4] used umbrathor for pyelography in three cases, and found that no harm was done. Radt [2] reported that his dogs were healthy one and three-quarter years after the first injection of tordiol, with the spleen and liver macroscopically normal and showing no noteworthy histologic changes. He did, however, observe the same transient changes in the blood that have been mentioned, but no changes in blood chemistry. He found much the same results in his patients, some having brief chills. Jaffé [5] had, at this time, already sounded a general warning against such colloidal preparations.

Tsunoo and Nakamura [6] found the formation of bilirubin greatly decreased or totally absent for two or three weeks after the injection of thorotrast. Kadrnka [7]

From the Department of Obstetrics and Gynecology of the University of Chicago.

1. Bluhbaum, T.; Frik, K., and Kalkbrenner, H.: Fortschr. a. d. Geb. d. Röntgenstrahlen **37**:18, 1928.
2. Radt, P.: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **43**:443, 1931; Klin. Wchnschr. **8**:2128, 1929; Med. Klin. **26**:1888, 1930.
3. Oka, M.: Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:497, 1929.
4. von Adler-Racz, A.: Ztschr. f. urol. Chir. **29**:533, 1930.
5. Jaffé, R.: Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:692, 1929.
6. Tsunoo, S., and Nakamura, H.: J. Biochem. **12**:133, 1930.
7. Kadrnka, S.: Schweiz. med. Wchnschr. **61**:425, 1931; Fortschr. a. d. Geb. d. Röntgenstrahlen **44**:9, 1931; Radiology **18**:371, 1932.

at first was unable to find any cell changes with the doses of thorotrast that he used. He stated that the hemoglobinuria observed in many dogs was not produced in the human being, and that the results of liver function tests remained unchanged. With larger doses, however, he produced hyaline degeneration in the glomeruli and some necrosis of the hepatic cells. Pregnancy was not disturbed. Volicer [8] used the drug in ten patients and found no evidence of damage.

Einhorn, Stewart and Illick [9] reported some bad reactions due to thorotrast in their patients, e.g., fever, excessive perspiration, weakness, and even hematemesis in one case of Banti's disease. Lambin [10] thoroughly described characteristic blood changes—anemia, brief leukopenia, followed by relative lymphocytosis and later polynucleosis. Kadrnka and Rossier [11] gave a detailed account of tissue changes in animals given injections of thorotrast, as did Baumann and Schilling,[12] Popper and Klein,[13] Huguenin, Nemours and Albot [14] and Randerath.[15] Kadrnka [7] noted occasional vomiting in patients with cirrhosis or nephritis, a fit of coughing in an asthmatic person, and a slight hemoclastic shock in a patient who had chronic splenomegaly, on using thorotrast. Popper and Klein [13] found no significant changes in dogs watched for a month. Radt [2] later found persons with cirrhosis or leukemia who did not tolerate the drug well, showing fever and small generalized disturbances.

Shih and Jung [16] had one pregnant rabbit abort after a dose of 0.5 cc. per kilogram on two consecutive days. Two of their rabbits showed petechiae in the lungs and renal cortices, with platelet reduction. With larger doses they found a greater decrease in platelets, marked delay in the bleeding time, moderate delay in the clotting time and poor clot retraction. Several animals showed weakness, and all of them showed much extravasation of blood into the tissues at autopsy. One animal had hemoptysis and bled freely from abrasions. They concluded that thorotrast produced acute purpura hemorrhagica, and that amounts three or more times the standard dose were usually fatal. Held [17] found no influence of the drug on the formation of defense mechanisms, such as hemolysins, but an undoubted effect on antibodies already present.

Büngeler and Krautwig [18] reported a case of spontaneous rupture of the spleen, secondary to necrosis developing twenty hours after the second of two daily injections of thorotrast, and noted increased friability of all tissues. At autopsy there were many splenic thrombi. They concluded that such thorium preparations were highly dangerous and had no place in either therapy or diagnosis. Tripoli, Haam and Lehman [19] used thorotrast safely in fifteen patients.

Stewart, Einhorn and Illick [20] observed no sequelae of interest in five of eight cases, vomiting for several days in three after the second injection, and hemor-

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8. Volicer, L.: Fortschr. a. d. Geb. d. Röntgenstrahlen **44**:452, 1931.
9. Einhorn, M.; Stewart, W., and Illick, H.: M. J. & Rec. **134**:56, 1931.
10. Lambin, P.: Compt. rend. Soc. de biol. **109**:66, 1932; **108**:264, 1931.
11. Kadrnka, S., and Rossier, J.: Acta radiol. **12**:369, 1931.
12. Baumann, H., and Schilling, C.: Klin. Wchnschr. **10**:1249, 1931.
13. Popper, H., and Klein, E.: München. med. Wchnschr. **78**:1829, 1931.
14. Huguenin, R.; Nemours, A., and Albot, E.: Compt. rend. Soc. de biol. **108**:879, 1931.
15. Randerath, E.: Klin. Wchnschr. **11**:144, 1932.
16. Shih, H., and Jung, T.: Proc. Soc. Exper. Biol. & Med. **29**:243, 1931.
17. Held, A.: Klin. Wchnschr. **11**:463, 1932.
18. Büngler, W., and Krautwig, J.: Klin. Wchnschr. **11**:142, 1932.
19. Tripoli, C.; Haam, E., and Lehman, E.: Am. J. Roentgenol. **27**:265, 1932.
20. Stewart, W.; Einhorn, M., and Illick, H.: Am. J. Roentgenol. **27**:53, 1932.

rhages in two. In four cases that came to autopsy they found acute splenitis, but it is questionable if this can be unhesitatingly ascribed to the thorotrast used. They stated that "except in unusual cases the test does not seem to yield enough independent information to justify its use." Kadrnka [7] recently advised against its routine use, especially in young persons, and suggested that it be limited to cases of carcinoma, ecchinococcus cysts, or abscesses of the liver and spleen, especially cases in which one plans to intervene later. Ehrhardt [21] was never able to get a mouse that had been treated with this drug pregnant. Kadrnka and Rossier [11] had one rabbit that delivered normal young at term three days after injection. Lewisohn [22] used thorotrast on six patients, of whom four had advanced carcinomas, and found no ill effects. Two of his rabbits died soon after relatively small doses, and two more died at eighteen and twenty-six days. One of the four rats used by Menville and Ané [23] died twenty-four hours after the injection of a relatively large dose. Harris and Friedrichs [24] used large doses in rats and had a mortality of 4 per cent, but those that lived seemed healthy for months.

Kadrnka [7] found the density of the splenic shadow decreased by one half in three months' time. Bluhbaum, Frik and Kalkbrenner [1] found the shadow unchanged after a period of months. Popper and Klein [13] stated that their dogs showed no change in the intensity of the shadow of the liver and spleen in seven months, and human beings, none in four months. Beutel [25] reported a case in which the shadow of the liver and spleen was unchanged after seven months. Stewart, Einhorn and Illick [20] found no change in the density of the shadow in one case followed for eight months. Huguenin, Nemours and Albot [14] found granules of thorium in tissues as long as nine months after injection. Kadrnka and Rossier [11] reported the opacity of the liver and spleen unchanged in a rabbit in the first two months, but reduced to one half in four months.

The tissue changes following the administration of these colloidal thorium preparations have been well described. After ordinary doses the reticulo-endothelial cells of the liver and spleen show much cloudy swelling, loss of staining, and the presence of irregular-sized granules and droplets of thorium. These are colorless and highly refractile. The malpighian corpuscles of the spleen diminish in size. Popper and Klein [13] noted hemosiderosis of the spleen in one case and in another an increase of leukocytes in the hepatic capillaries. The Kupffer cells of the liver are much swollen and filled with thorium twenty-four hours after the injection. The same is also true of the reticulo-endothelial cells of the spleen.

Baumann and Schilling [12] found the Kupffer cells swollen to the size of hepatic cells some fourteen days after injection. The nucleus of the swollen cell is eccentric and flattened. Many large polygonal cells in the splenic pulp become loaded with thorium. There is no thorium in the capillary endothelium. There are many cosinophilic cells in the spleen and bone marrow. Thorium particles are also

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21. Ehrhardt, K.: Klin. Wchnschr. **11**:332, 1932.

22. Lewisohn, R.: Surg., Gynec. & Obst. **55**:68, 1932.

23. Menville, L., and Ané, J.: Proc. Soc. Exper. Biol. & Med. **29**:1045, 1932.

24. Harris, W., and Friedrichs, A.: Proc. Soc. Exper. Biol. & Med. **29**:1047, 1932.

25. Beutel, A.: Med. Klin. **28**:112, 1932.

present in the reticular cells of the bone marrow. Giant cells soon appear in the spleen and liver, and the liver may show infiltration by small round cells. The occasional reticular cells of the lymph follicles of the spleen also show granules, and it has even been suggested that the picture somewhat resembles Gaucher's splenomegaly.

Kadrnka [7] observed necrosis of the hepatic cells when his doses were increased to 10 cc. per kilogram, but Lambin [10] believed even 5 cc. per kilogram had a marked effect on the splenic pulp and parenchymatous cells of the liver. With very large doses, Lambin found that the parenchyma of the liver was almost entirely replaced by a mass of fibrosis, with many histiocytes and giant cells full of thorium. There was no trace of hematopoietic tissue in the middle of the femur in such cases, but the costal marrow was not so much changed. Even the pulmonary septums, kidneys and suprarenal glands showed a few histiocytes. No reticulo-endothelial block is produced, according to Kadrnka [7] and others. In large doses Kadrnka [7] noted some hyalinization of the renal glomeruli and small areas of necrosis in the liver, but he emphasized the fact that these developed only after doses fifteen or twenty times that ordinarily used. Fatty degeneration is seen in some cells of the liver and the kidneys. Cancer cells do not pick up the thorium, but lymph nodes do to some extent.

Randerath [15] found very small amounts in the cortices of the suprarenal glands, hypophysis, pancreas, thyroid gland, brain, heart, aorta, lungs and bronchi, tongue, esophagus, intestine, mesenteric and subcutaneous fat, gallbladder, ureters, bladder, prostate, seminal vesicles, rectum and muscles of the extremities. Harris and Friedrichs [24] noted that the damage produced by thorium in the viscera is more widespread than in the reticulo-endothelial cells alone.

A year and a half ago we began to use thorium preparations in an effort to visualize roentgenologically the placentas of dogs and rabbits. We employed umbrathor and a preparation made for us by Dr. Marberg of the Otho A. Sprague Institute. This preparation resembled umbrathor, was very slightly acid, and relatively clear and stable. We do not describe its preparation because we feel it is as dangerous as other such preparations and has no advantages over umbrathor or thorotrast, which we have recently used exclusively. Our experience in this regard corresponds to that of Berberich, Büngeler and Kleeberg (see Büngeler and Krautwig [18]). Our material consisted of sixteen dogs and twelve rabbits. Three of the dogs were followed for as long as one hundred and six days after injection. Of these animals, one dog and seven rabbits were pregnant. We injected varying doses of the material.

The pregnant animals, with the exception of one rabbit, carried their young to term or had them removed very near term by cesarean operation. The dog delivered its young four days after injection, and the rabbits, in from one to thirteen days. The young animals lived up to thirty-six hours before they were killed for this study. All seemed normal during that time.

One pregnant 3 Kg. rabbit delivered its young prematurely some twelve hours after the intravenous administration of 17 cc. of thorotrast. The young appeared normal, but the mother died from a postpartum hemorrhage, and at autopsy a minute spontaneous rupture of the spleen

at the inferior pole was found. There was no other intra-abdominal hemorrhage, but much blood was found in the uterine cavity. This case is strongly reminiscent of the one reported by Büngeler and Krautwig.[18] We found no evidence of hemorrhages into the tissues in our other animals. In all our animals there was a very obvious increase in the friability of the viscera, especially of the spleen. At times this organ

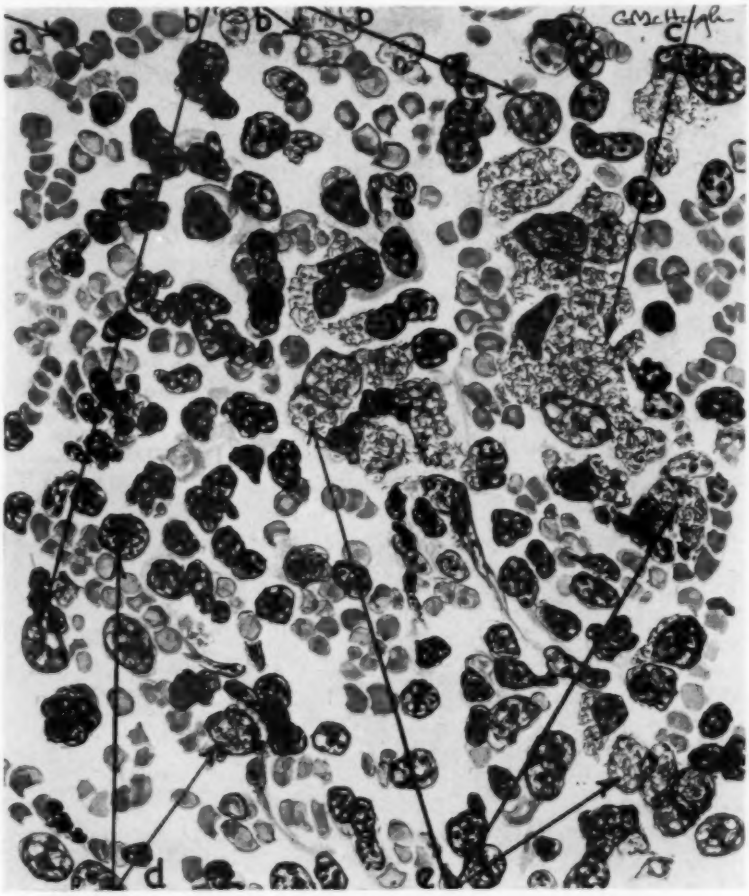

Fig. 1.—Rabbit spleen eleven days after injection of thorotrast. The arrows point out (*a*) red blood cells; (*b*) swollen, degenerating reticular cells; (*c*) free particles of thorium; (*d*) relatively normal reticulo-endothelial cells containing thorium; (*e*) acutely degenerating macrophages containing thorium.

could scarcely be handled on this account. The liver and the spleen rapidly assume the gross appearance of cloudy swelling.

We have spent considerable time in attempting to stain the thorium particles in the tissues, with complete lack of success. Various authors

have suggested that the particles show up best in tissues stained with aniline blue, van Gieson's stain, etc., but we have found simple congo red or Harris' hematoxylin alone to be best. The thorium particles appear to be highly refractile, but are definitely not doubly refractile.

Very soon after injection the thorium takes the form of irregular translucent droplets of all sizes, but in a few days any of it ingested by the cells is in the form of minute particles. We have been much impressed by the intense and widespread degeneration of viscera, such as the liver and spleen (fig. 1), which absorb the bulk of this material, and we do not believe that this has been emphasized sufficiently in previous reports. It is difficult to see how anyone can recommend its clinical use after seeing the microscopic changes produced within a few hours or days after its administration. However, our animals showed few symptoms of distress. The dogs observed for two or three months seemed healthy during that time, and we were amazed at the thoroughness with which the spleen and liver recovered in these animals in such a short time. In three months there was practically no evidence of thorium in the spleen and liver. What particles were present were aggregated in isolated cells and had assumed a much darker amber color. The great bulk of the reticulo-endothelial and pulp cells were normal in size and relation, but very pale-staining.

We were unable to secure placental visualization in our animals with doses of these preparations at all commensurate with the preservation of maternal tissues. We administered as much as 6 cc. per kilogram in divided or single doses. However, Ehrhardt [21] and Menville and Ané [23] recently visualized the placentas of mice and albino rats, respectively, with relatively enormous doses. The doses used by Menville and Ané to secure successful placental visualization were approximately from four to six times the relative dose that proved fatal to the pregnant rabbit mentioned in our series. Katsuya [26] reported visualization of the placenta of rats, guinea-pigs and rabbits. He used in his rabbits even smaller doses than we used. Ehrhardt could not visualize the human placenta in situ. He found the thorium retained for only one month in the liver and spleen of the mouse, but could never get such a mouse pregnant and could never visualize the fetal liver or spleen. Menville and Ané confirmed the absence of thorium in the fetuses, as we also can. Roentgenograms of the fetuses and careful histologic studies of their viscera revealed neither thorium particles nor any of the characteristic degenerations. The placenta is, therefore, a most effective barrier, in the dog and rabbit at least, to the passage of colloidal suspensions of thorium.

Although the placentas of four animals did not contain sufficient thorium for roentgenologic visualization, the metal could be found in

26. Katsuya, S.: Jap. J. Obst. & Gynec. **15**:77, 1932.

them histologically up to eleven days after injection. The maximum amount of the colloidal suspension was present in the placental cells of the rabbit from four to seven days after injection (fig. 2) and had entirely disappeared thirteen days after injection. The fetal portion of the rabbit placenta near term is composed entirely of tubules consisting

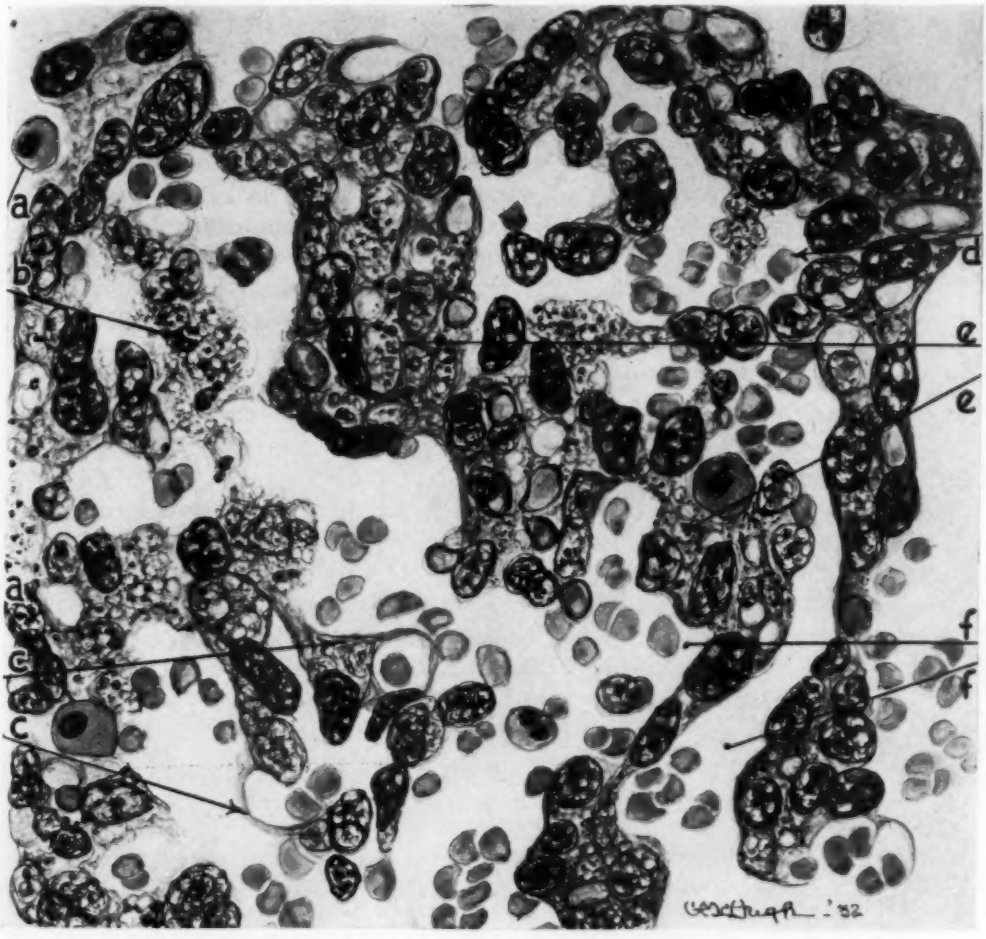

Fig. 2.—Rabbit placenta seven days after injection of thorotrast. The arrows point out (*a*) normoblasts; (*b*) thorium particles; (*c*) endothelium separating fetal and maternal vascular channels; (*d*) red blood cells; (*e*) thorium particles in plasmodial cytoplasm; (*f*) fetal and maternal vascular channels.

of plasmodial cells and vascular channels, and these correspond to the villi of the human placenta. Twenty-four hours after injection the thorium particles were not well localized in the placenta, but by the time four days had elapsed, the characteristic large globules had been replaced

by small punctate particles scattered in patches throughout the cytoplasm of these plasmodial cells. There seemed to be little of the thorium, if any, in the nuclei. A characteristic peppered appearance was produced in these cells. We never observed the characteristic degeneration of cells that would be analogous to that seen in the cells of the liver, spleen, etc., shortly after injection. The decidual portions of the placenta and the sinus and intermediate layers showed practically no thorium particles at any time.

SUMMARY AND CONCLUSIONS

By means of intravenous injections of thorotrast and similar thorium preparations, we secured the visualization of the spleen and liver in rabbits and dogs, but were unable to visualize the placenta. We used smaller relative doses than other authors did for successful placental visualization in the rat. These doses, however, produced intense degeneration, particularly of the liver and spleen, caused one of our rabbits to abort, and produced spontaneous rupture of the spleen as well as a fatal postpartum hemorrhage in this animal. At present colloidal thorium preparations have no place in clinical work.

Particles of thorotrast practically disappear from the liver and spleen in two or three months after their injection, and the cells by that time regain almost a normal appearance.

The placenta of the dog and of the rabbit appears to be an effective barrier to the transmission of thorium to the fetus. With the exception of the animal mentioned, all of our pregnant animals carried their young to term or were killed near term for this study.

The metal could be found in the rabbit placenta microscopically up to eleven days after injection, but by this time it was in the form of very fine particles and after that seemed to disappear. We were unable to stain the thorium particles in the tissues. The placental cells do not show the destructive changes seen in the cells of the liver and spleen.

NECROTIZING ARTERITIS AND SUBACUTE GLOMERULONEPHRITIS IN GONOCOCCIC ENDOCARDITIS

TOXIC ORIGIN OF PERIARTERITIS NODOSA

MILTON HELPERN, M.D.
AND
MAX TRUBEK, M.D.
NEW YORK

There is considerable difference of opinion concerning the origin of the necrotizing, nonsuppurative inflammatory arterial lesions usually designated as periarteritis nodosa. Whether these lesions are a disease of the blood vessels, *sui generis*, caused by a specific bacterial agent or virus, or whether they represent a specific vascular reaction to any of a great variety of toxic agents, is as yet unsettled. The following combination of findings clearly strengthens the conception of the nonspecific toxic origin of these lesions.

REPORT OF CASE

Clinical History.—A white man, aged 25, unmarried, a chauffeur, was admitted to the Fourth Medical Division of Bellevue Hospital, in the service of Dr. Alexander Lambert, on March 19, 1931, and died seven days later. He complained of generalized edema, which first appeared in his ankles nine weeks before and quickly spread over the entire body. Weakness, polyuria and dyspnea were present. There was no history of operations, tonsillitis, rheumatism or scarlet fever. The patient had previously been healthy.

However, early in November, 1930, about nine weeks before the edema began, the patient contracted gonorrhea, followed shortly after by involvement of the left eye, for which he was treated in the eye service of Bellevue Hospital for four weeks (November 24 to December 20). The diagnosis of gonococcic ophthalmia was confirmed by Gram-stained smears of the conjunctival pus. At that time the right eye and fundus were normal. The left fundus could not be seen. In the left cornea an ulceration developed that subsequently healed over. With treatment, the conjunctival discharge diminished, and the gonococci disappeared. The laboratory findings at that time were as follows: urine, on admission, normal; nonprotein nitrogen of the blood, 34 mg. per hundred cubic centimeters; Wassermann reaction of the blood, negative.

The temperature curve was unusual for gonococcic ophthalmia. During the entire four weeks there were fluctuations between 99 and 101 and occasionally 101.8 F. The pulse rate varied between 80 and 120. The night before the patient was discharged from the eye service the temperature was 100.8 F. During the three weeks' interval before the onset of the edema the patient said he felt well.

From the Pathological Laboratories and Fourth Medical Division of Bellevue Hospital.

On admission to the medical ward, twelve weeks after discharge from the ophthalmic ward, he appeared acutely ill, very pale, drowsy, dyspneic and orthopneic. There was generalized anasarca. The heart was moderately enlarged to the left. Reduplication of the second sound was noted at the apex, with a short systolic murmur over the base. The left cornea was opaque. The right fundus showed papilledema and flame-shaped hemorrhages. The systolic blood pressure was 174 mm. and the diastolic 102 mm. Successive urinalyses showed a cloudy, yellow, acid fluid, the specific gravity varying between 1.010 and 1.014, a large amount of albumin, granular and white blood cell casts and red and white blood cells. The nonprotein nitrogen of the blood was 81 mg.; creatinine, 3 mg.; sugar, 90 mg.; cholesterol, 180 mg., and chlorides, 643 mg. The blood count revealed 1,700,000 red cells with 15 per cent hemoglobin, and 18,200 white cells with 88 per cent polymorphonuclears. The Wassermann reaction of the blood was again negative. The urinary sediment contained doubly refractile lipoids.

The patient became progressively worse. On the third day, the blood pressure was 154 mm. systolic and 94 mm. diastolic. On the fifth day, a pericardial friction rub was heard. The urine was unchanged, except that larger numbers of white blood cells were found in an uncatheterized specimen, but this was explained on the basis of a severe balanitis which developed in the edematous foreskin. A smear of the uncatheterized urinary sediment revealed gram-positive cocci; no gram-negative forms were noted. The possibility of a general infection by the gonococcus was considered at that time. A blood culture was negative. On the sixth day, several small petechiae were noted on the shoulders. The blood pressure fell to 140 mm. systolic and 92 mm. diastolic. The nonprotein nitrogen rose to 100 mg. and the creatinine to 4.3 mg. per hundred cubic centimeters. The carbon dioxide-combining power was 29 per cent by volume. The temperature during the illness fluctuated between 98 and 100.4 F.; the pulse rate, between 110 and 145. The patient became stuporous and comatose and died on the seventh day. The clinical diagnosis was glomerulonephritis and uremia with pericarditis.

Autopsy.—Necropsy, performed twelve hours after death, disclosed generalized anasarca. No petechiae were found. The left cornea was opaque. The abdominal cavity contained 2 liters and each pleural cavity contained 1 liter of clear fluid. The lungs were edematous and covered with a layer of fibrin, most abundant over the right lower lobe, which was adherent to the wall of the chest. There was a fresh fibrinous pericarditis with 200 cc. of clear yellow fluid in the sac. The heart weighed 430 Gm. and showed moderate hypertrophy of the left ventricle. The pulmonic valve was the site of an ulcerating, vegetative endocarditis (fig. 1). There were small, friable, granular and flat, adherent vegetations on all the cusps, extending from the valve up on the pulmonary artery and also down on the endocardium of the right ventricle. The edges of the valve cusps were irregularly eaten away. Above the valve, in the vicinity of the vegetation, the lining of the pulmonary artery was roughened and scarred. The remaining valves of the heart were normal except for slight atheroma in the aortic valve and the aortic leaflet of the mitral valve. The coronary arteries were thin-walled. The aorta was narrow, smooth and elastic. The liver weighed 2,420 Gm. and showed passive congestion. The spleen was enlarged, measuring 12 by 17 by 7 cm., and weighed 570 Gm.; on section, the pulp was pale red and friable, and the follicles were prominent. The kidneys together weighed 550 Gm. Each organ measured 13 by 8 by 5 cm. The capsules stripped easily, and the surfaces were smooth yellowish gray; no hemorrhages were noted. On section, the cortex measured 12 mm. and was obviously widened; the markings were exaggerated, with alternately placed yellowish and reddish-gray streaks. The glomeruli were enlarged and visible; the

medulla, reddish gray; the pelves were congested and slightly thickened; the blood vessels were normal. The bladder contained 800 cc. of urine; the ureters were normal. The prostate was small, and the periprostatic plexus of veins distended with soft, red thrombi. The seminal vesicles were normal. The testes were somewhat smaller than normal, but showed no other change to the naked eye. The brain and its blood vessels were normal except for slight pial edema. The middle ears, mastoids and nasal sinuses were normal. The posterior half of the right eyeball was removed. There was retinal edema around the optic disk, and there was a small retinal hemorrhage between the disk and the macula measuring about 1 mm.

Microscopic Examination.—Smears of crushed vegetations from the pulmonic valve at the time of autopsy revealed small numbers of gram-negative, biscuit-

Fig. 1.—Subacute vegetative endocarditis of the pulmonic valve. There is extension to the pulmonary artery and the right ventricular endocardium. The edges of the valve are irregularly ulcerated.

shaped diplococci; cultures were unsuccessful. Sections through the pulmonic valve revealed a subacute vegetative endocarditis (fig. 2). There were superficial thrombotic masses composed of fibrin and polymorphonuclear leukocytes in large numbers. In Giemsa-stained sections, the latter contained numerous diplococci, which proved to be gram-negative in other sections stained with a controlled modification of the Gram stain.[1] No other micro-organisms were found. At the base of the vegetations, there was active organization by vascular granulation tissue growing from the valve (fig. 2*a*). There was a gradual transition from the cellular and vascularized granulation tissue in the superficial layers of the valve to a more fibrous granulation tissue which produced considerable thickening of the valve (fig. 2*b*). Small masses of adherent vegetation were also attached to the roughened intima of the pulmonary artery a short distance above the valve. The

1. Brown, J. H., and Brenn, L.: J. Bact. **21**:21, 1931.

underlying media was thickened, and in the adventitia there was a small amount of cellular granulation tissue composed of capillaries showing perivascular leukocytic and round cell infiltration (fig. 2*c*). The muscle fibers beneath the endocardium of the right ventricle where the vegetations were found were infiltrated with polymorphonuclear leukocytes. The myocardium elsewhere, chiefly in the right ventricle, contained scattered small interstitial foci of polymorphonuclear leukocytes without organisms. Sections through the remaining valves and papillary muscles were normal. The epicardium was covered with a thin layer of fibrinous and polymorphonuclear cell exudate, also bacteria-free. In the subepicardial fat overlying the pulmonary artery, numerous plasma cells were found. The larger coronary arteries showed slight eccentric intimal hyperplasia. In only one of numerous sections of the heart did the media of a small-sized artery exhibit a slightly homogeneous appearance, suggestive of fibrinoid necrosis.

Sections of the lungs revealed areas of infarction over which the pleura was thickened and covered with a layer of organizing fibrin. The smaller branches of the pulmonary artery entering the infarcted zones were occluded by cellular granu-

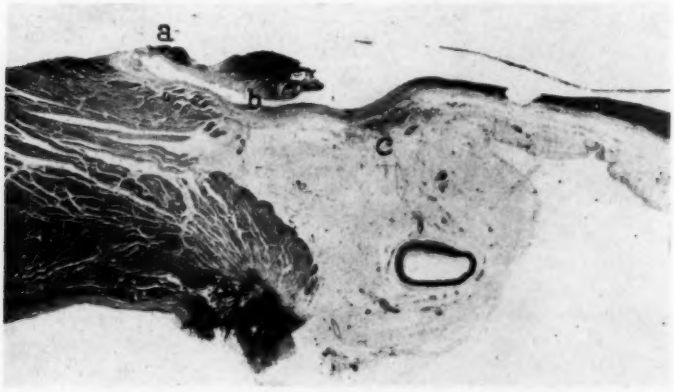

Fig. 2.—Section through a pulmonic valve cusp with vegetation. At *a* is a mass of fibrinous vegetation undergoing active organization where it is attached to the valve cusp; superficial layers of polymorphonuclear leukocytes contain gram-negative diplococci. At *b* is older and more fibrous granulation tissue resulting from progressive organization of the vegetation. At *c* is an area of granulation tissue in the adventitia of the pulmonary artery; hematoxylin and eosin; × 4.

lation tissue representing the organization of emboli from the pulmonic valve. The walls of the blood vessels were not abnormal. The remaining parenchyma was congested and edematous.

Frozen sections of the kidneys stained with sudan III and hematoxylin revealed abundant lipoid in the convoluted tubules. This lipoid was doubly refractile. Numerous sections of both kidneys stained with hematoxylin and eosin and with Giemsa stain revealed a diffuse and severe, active subacute glomerulonephritis chiefly of the capsular type. All the glomeruli exhibited large, thick cellular crescents, which in places completely encircled the capsular spaces (fig. 3). Most of the tufts showed increased cellularity, fusion and opacity. This intracapillary process was overshadowed by the capsular proliferation. In a few glomeruli, the crescents and tufts were beginning to undergo fibrosis; in several, hemorrhages into the capsular space were seen.

The tubules were decreased in number and severely distorted with dilatation, compression and atrophy of the lining epithelium. Numerous hyaline casts and also leukocytic casts were found. In places the tubules contained red blood cells.

The interstitial connective tissue was distinctly increased and contained numerous congested capillaries. The parenchymatous elements were widely separated by this process. Careful examination of the blood vessels in numerous sections disclosed no changes in the afferent arterioles and interlobular arteries. No necrotizing lesions were found. A mild eccentrically placed intimal hyperplasia was noticed in the larger arteries. No bacteria were found in the kidney.

In the testis, unsuspected striking alterations were found in all the small arteries. These were easily visible even in very low magnification (fig. 4). In sections stained with hematoxylin and eosin, the medial and adventitial coats of the vessels were intensely and uniformly eosinophilic. These layers appeared

Fig. 3.—Subacute glomerulonephritis: glomerulitis with characteristic crescentic capsular proliferation; atrophy and degeneration of tubules; proliferation of interstitial tissue. Numerous sections through the kidney do not reveal any significant vascular lesions; 16 mm. objective; hematoxylin and eosin.

thickened and necrotic (fig. 5). In some of the vessels, the necrosis was eccentrically distributed, and small particles of nuclear débris were found in the necrotic zones. Varying degrees of intimal hyperplasia, in places resulting in complete occlusion and recanalization of the lumen, were found (fig. 6). A mild subendothelial leukocytic infiltration was present in the intima, and a very slight infiltration of polymorphonuclear leukocytes in the media and adventitia. In sections stained with Mallory's connective tissue stain and with Weigert's fibrin stain, the media and adventitia stained like fibrin, the latter substance extending beyond the adventitia. Although aneurysms were not found, the thickened vessels appeared dilated. Sections stained with Weigert's elastic tissue stain showed partial destruction of the elastica interna (fig. 7). The seminiferous tubules were atrophied,

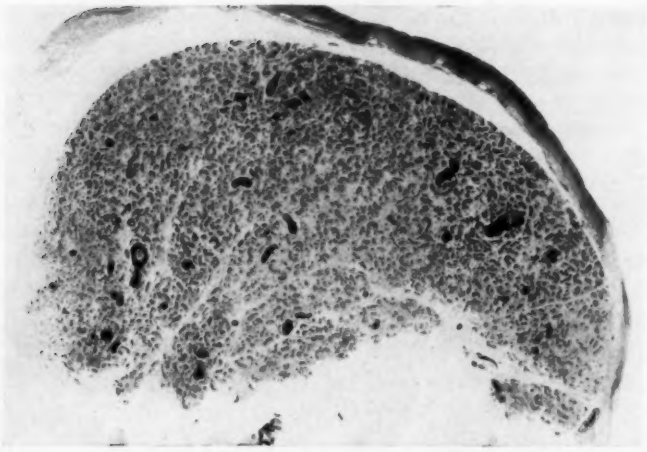

Fig. 4.—Section of a testis. All the arteries are thick-walled and abnormally prominent, staining intensely with eosin. The seminiferous tubules are atrophied, and the interstitial tissue is increased; hematoxylin and eosin; × 4.

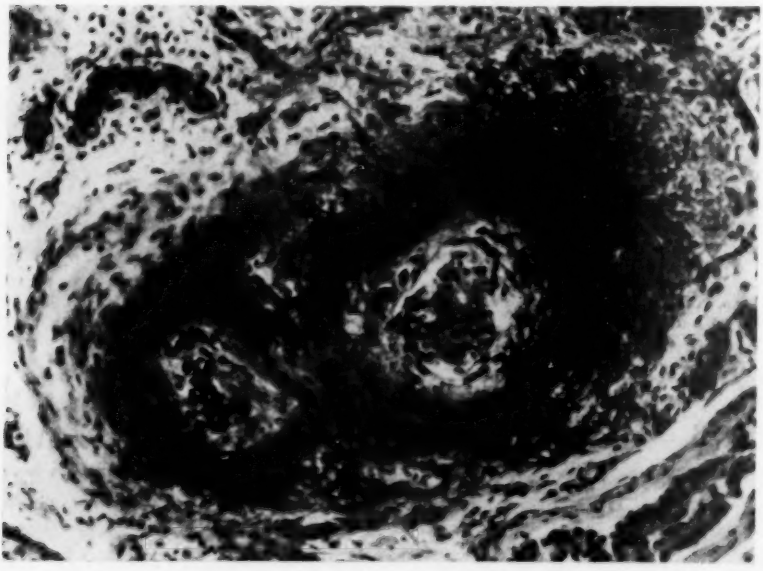

Fig. 5.—Artery of a testis. The media and the adventitia are replaced by a thickened, homogeneous necrotic layer staining like fibrin. This layer extends beyond the adventitia and is infiltrated by a small number of polymorphonuclear cells. There is intimal hyperplasia with narrowing of the lumen; 8 mm. objective; hematoxylin and eosin.

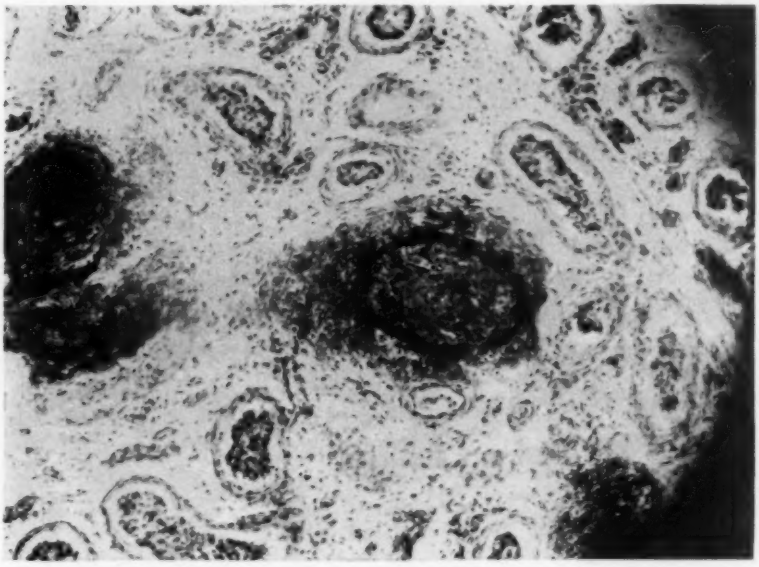

Fig. 6.—An affected artery of a testis, showing obliterated and canalized lumen; 16 mm. objective; hematoxylin and eosin.

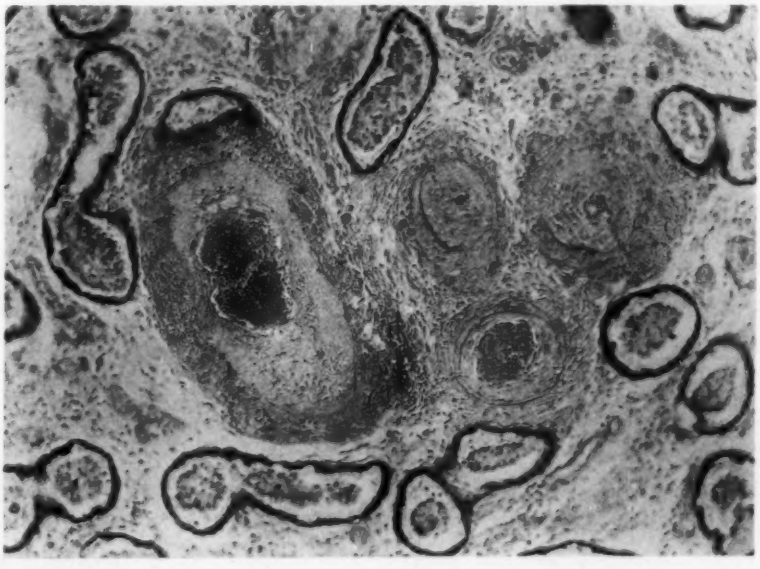

Fig. 7.—Group of blood vessels showing interruptions and destruction of the internal elastic lamina. There is marked intimal hyperplasia; 16 mm. objective; Weigert elastica stain.

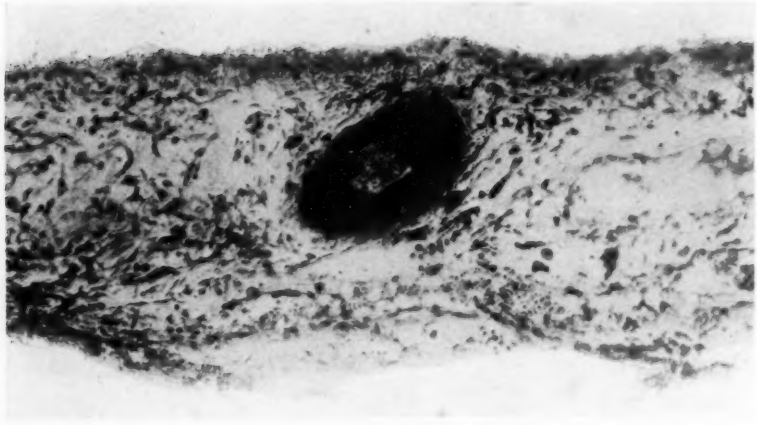

Fig. 8.—Choroid coat of an eye. The arterial wall shows a necrotizing process similar to that seen in the testis. There is edematous thickening of the choroid coat; 8 mm. objective; hematoxylin and eosin.

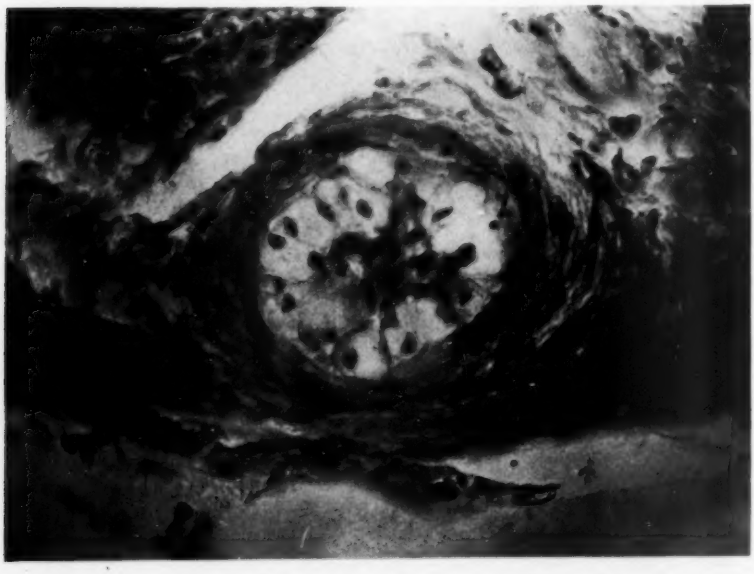

Fig. 9.—Artery in the choroid coat. The swollen, vacuolated endothelial cells are polyhedral in outline. There is a fibrinoid substance in the lumen and between the endothelial cells; 4 mm. objective; hematoxylin and eosin.

and the interstitial tissue was slightly increased. Unfortunately only one block of testis was saved for microscopic study. The epididymis was not examined. Sections of the testis did not contain any bacteria.

Section through the posterior half of the right eye revealed retinal edema over the disk. The walls of the retinal vessels including the central artery of the retina in the optic nerve showed no change. The choroid coat was thickened, and the choroidal blood vessels exhibited profound changes. These were readily seen on low magnification. Many of the arteries showed changes identical with those of the vessels in the testis. The media was thickened and necrotic and replaced by a fibrinous substance extending out to the adventitia (fig. 8). In addition, certain arteries exhibited a curious swelling of the endothelial cells, the latter having a transparent polyhedral, almost glandlike appearance. In these vessels, a homogeneous reddish-staining fibrinoid substance was present in the lumen and between

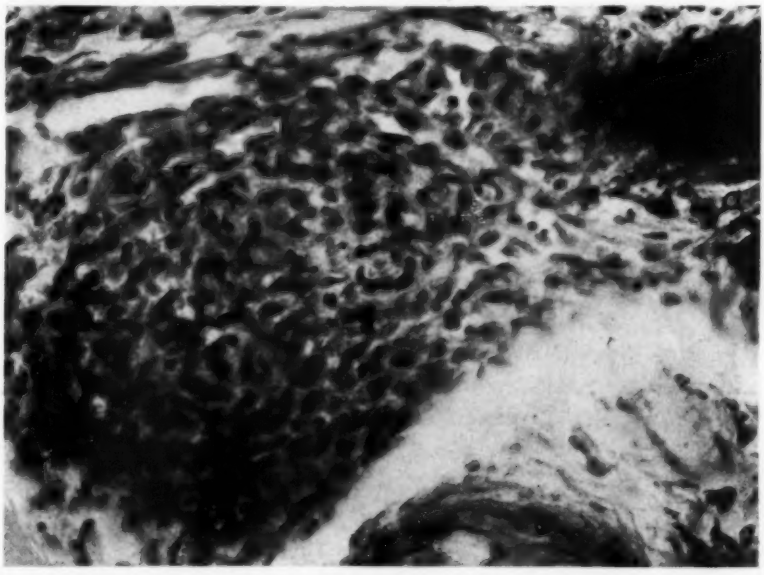

Fig. 10.—Granulomatous nodule in the choroid. There is a circumscribed proliferation of fibroblasts and endothelial cells with slight polymorphonuclear cell infiltration and new capillary formation. The nodule is continuous with the wall of a necrotic artery at *a* similar to that shown in figure 8; 4 mm. objective; hematoxylin and eosin.

the endothelial cells (fig. 9). Adjacent to, and apparently associated with, some of the necrotic arteries, small granulomatous-like nodules were found, composed of fibroblasts and endothelial cells with a scant infiltration by polymorphonuclear leukocytes and capillary formation (fig. 10).

Sections stained with Weigert's elastic tissue stain revealed destruction of the elastica in the necrotic vessels and preservation of the elastica in the vessels with the swollen endothelium. In the necrotic vessels adjacent to the nodule, the elastica became lost in the portion of the nodule adjoining the vessel. All the ocular vascular lesions were bacteria-free.

Sections of the prostate, spleen, suprarenal glands, aorta, larger arteries and lymph nodes did not reveal any vascular lesions. The skeletal muscles and peripheral nerves were not examined.

COMMENT

The histologic features of the vascular lesions in the choroid coat and the testis in the case described conform to many of those that are characteristic of periarteritis nodosa so well enumerated by Wohlwill.[2] Thus, medial fibrinoid necrosis, disintegration of elastica interna, subendothelial intimal proliferation resulting in fibroblastic obliteration and canalization of the lumen, vacuolation of the endothelial cells, eccentric involvement of the walls of vessels, absence of suppuration and the occasional periarteritic nodule were present. A few of the more frequent findings were absent: thromboses, true aneurysms of the walls of vessels, and an abundant cellular infiltration of the coats and periadventitial regions.

In the fully developed lesions of periarteritis nodosa medial necrosis is always present, transforming that layer into a homogeneous eosinophilic substance resembling fibrin in its staining characteristics. This medial reaction was the most striking lesion in the vessels in the case described, and although periadventitial cellular infiltration was absent, there was abundant fibrinous exudate within and beyond the adventitial layer.

The gross anatomic requirements of the original description of periarteritis nodosa by Kussmaul and Maier [3] have not always been fulfilled. In subsequent cases of this disease, even in the absence of gross lesions, the histologic criteria have formed a basis for identification. With a more detailed study of arterial alterations in other diseases, similar significant medial lesions have been observed.

Siegmund [4] noted arterial lesions identical with those of periarteritis nodosa in streptococcic sepsis lenta of long duration. Strang and Semsroth [5] recently reiterated the importance of "low virulence" in chronic streptococcic sepsis for the production of this reaction, and in their own case described necrotizing lesions in the valves of the heart and the arteries of the kidneys. Klinge and Vaubel [6] often found it difficult to distinguish between certain arteritic lesions occurring in rheumatic fever characterized by "fibrinoid degeneration" and similar changes occurring in periarteritis nodosa. Fahr [7] did not believe that too sharp a differentiation should be made between the necrotizing arteritis of

2. Wohlwill, F.: Virchows Arch. f. path. Anat. **246**:377, 1923.
3. Kussmaul, A., and Maier, R.: Deutsches Arch. f. klin. Med. **1**:484, 1866.
4. Siegmund, H.: Centralbl. f. allg. Path. u. path. Anat. **35**:276, 1924-1925.
5. Strang, J. M., and Semsroth, K.: Arch. Int. Med. **47**:582, 1931.
6. Klinge, F., and Vaubel, E.: Virchows Arch. f. path. Anat. **281**:701, 1931.
7. Fahr, T.: Virchows Arch. f. path. Anat. **248**:323, 1924.

the latter condition and the arteriolitis of malignant nephrosclerosis. Dawydowskie [8] described vascular lesions in typhus fever as identical with those of periarteritis nodosa. Plaut [9] recently directed attention to the important studies of Wiesel [10] and Wiesner [11] concerning the arterial changes occurring during infectious diseases and pointed out the confused state now existing concerning the classification of vascular lesions. Libman and Sacks [12] were aware of the widespread arterial lesions occurring in their cases of "atypical verrucous" endocarditis, lesions which in recent years have assumed an important rôle in the interpretation of that disease. Jores [13] suggested that the designation periarteritis nodosa will come to be a generic term for severe arteritides of infectious origin.

The similar septic clinical course of many of the patients suffering from periarteritis nodosa, together with the uniformity of the arterial damage, had suggested a single specific cause of the disease. This theory has had many supporters, among whom are Longcope,[14] Lamb,[15] Klotz [16] and Wohlwill.[2] The older conception of the syphilitic etiology as first suggested by Virchow,[17] from an examination of the material from the case of Kussmaul and Maier, has constantly lost ground. The absence of a history of syphilis in most instances, the occurrence of a positive Wassermann reaction in only a few cases, the repeated failure to demonstrate Spirochaeta pallida in any of the lesions and the distinctly different histologic nature of the two diseases are the evidence against syphilis being the specific cause.

Attempts to demonstrate a specific bacterial cause have been numerous. Streptococci and other micro-organisms have occasionally been identified in the lesion by cultural or tinctorial methods, and the occurrence of periarteritis nodosa directly after or associated with infections elsewhere in the body has been noted. Attempts to reproduce the disease experimentally by inoculation of micro-organisms, tissue filtrates or blood have in most instances been unsuccessful. These facts have been adequately given by Gruber [18] in his detailed review. The

8. Dawydowskie, J. W.: Ergebn. d. allg. Path. u. path. Anat. **20**:571, 1924.
9. Plaut, Alfred: Arch. Path. **14**:268, 1932.
10. Wiesel, J.: Ztschr. f. Heilk. **7**:262, 1906.
11. Wiesner, R.: Wien. klin. Wchnschr. **19**:725, 1906.
12. Libman, E., and Sacks, B.: Arch. Int. Med. **33**:701, 1924.
13. Jores, L.: Periarteritis Nodosa, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 652.
14. Longcope, W.: Bull. Ayer Clin. Lab., Pennsylvania Hosp. **5**:1, 1908.
15. Lamb, A. R.: Arch. Int. Med. **14**:841, 1914.
16. Klotz, O.: J. M. Research **164**:1, 1917.
17. Virchow, cited by Kussmaul and Maier.[3]
18. Gruber, G. B.: Virchows Arch. f. path. Anat. **258**:441, 1925.

reports of positive results by von Hann [19] and by Harris and Friedrichs [20] in their animal inoculation experiments were accepted by Arken,[21] without critical inquiry, as proof of the specific virus theory. Gerlach [22] produced similar lesions in sensitized animals by inoculation of serum, and Otani [23] repeated the animal inoculation experiments of von Hann,[19] using tissue and blood from persons showing typical cases of the disease, but obtained negative results and denied the possibility of a specific cause. Gruber considered the negative results obtained by Otani as significant and sharply criticized the work of Harris and Friedrichs, commenting on the absence of accompanying illustrations for certain statements and doubting the authenticity of their results.

A large group of authors including Spiro,[24] Robertson,[25] Otani,[23] Gruber [18] and Klemperer [26] have maintained that periarteritis nodosa is not a specific disease, *sui generis,* but rather a specific reaction occurring in previously sensitized arteries during the course of a variety of infectious diseases. This intense response, a form of bacterial allergy, is usually designated as "hyperergy." [27] Its occurrence is accidental either during a later stage of the same infection that originally sensitized the vessels or in a subsequent infection. According to Gruber,[18] the sensitizing infection need not be a severe one: coryza, suppurating wounds, furuncles, gonorrhea, syphilis, scarlatina, grip, lymphangitis, rheumatic fever and other conditions. In our case, the gonococcic toxin seems to have produced a characteristic arterial response, thus bearing out Gruber's surmise as to this micro-organism being a possible exciting cause. It is perhaps significant that the arterial lesions were found only in organs contiguous to the original purulent processes: the testicular lesion, in relation to the urethritis, and the choroidal involvement, in relation to the conjunctivitis. The proximity of the arterial lesions to the original infections might at first suggest a metastatic bacterial invasion. However, the type of inflammatory reaction is certainly not that produced by the presence of the gonococcus. This organism calls forth a purulent reaction, which was absent in the vascular lesions, but was present on the cardiac valve where the bacteria were identified. No bacteria were found in the vascular lesions, either in the eye or in the testis.

19. von Hann, F.: Virchows Arch. f. path. Anat. **227**:90, 1920.
20. Harris, W. H., and Friedrichs, A. V.: J. Exper. Med. **36**:219, 1922.
21. Arken, A.: Am. J. Path. **6**:401, 1930.
22. Gerlach, W.: Virchows Arch. f. path. Anat. **247**:294, 1923.
23. Otani, S.: Frankfurt. Ztschr. f. Path. **30**:13, 1924.
24. Spiro, P.: Virchows Arch. f. path. Anat. **227**:1, 1920.
25. Robertson, H. E.: Arch. Int. Med. **32**:870, 1923.
26. Klemperer, P.: Arch. Path. **13**:355, 1932.
27. Swift, H. F.; Derick, C. L., and Hitchcock, C. H.: J. A. M. A. **90**:906, 1928. Gerlach.[22]

The arterial lesions did not produce the manifestations of systemic disease but were, rather, isolated findings among those of a more obvious constitutional disorder. It is probable that the patient was already suffering from a general gonococcic infection when he was being treated for the ophthalmia. During that time, there was a moderate fever with mild septic fluctuation. Uncomplicated gonococcic ophthalmia is nearly always afebrile. That gonococcic endocarditis may run a relatively prolonged course has been pointed out by Thayer [28] and by Libman.[29] The histologic features of the valvular lesion in our case indicate an active process of relatively long duration, consistent with the stage of development of the renal lesion. The splenomegaly is confirmatory evidence of the prolonged course of the sepsis. The presence of organized emboli in the branches of the pulmonary artery supplying the infarcted areas also indicates that the valvular lesion had existed for some time.

The complication of toxic glomerulonephritis is not infrequent in gonococcic endocarditis, a fact which has been reported by Thayer [28] and by Baehr.[30] In our patient, the occurrence of the vegetations on the pulmonic valve is additional evidence for the toxic, rather than for the bacterial origin of the dissociated arterial and renal lesions. The febrile course following the patient's last admission together with the profound anemia suggested the presence of an active infection, in addition to the obvious glomerulonephritis, and the possibility of bacterial endocarditis was not dismissed on clinical examination.

The kidney is involved in periarteritis nodosa with greater frequency than any other organ. Gruber [18] was unable to distinguish any invariable picture of renal periarteritis nodosa. Our own finding of glomerulonephritis without the presence of any arterial lesions is significant. The toxic nature of this glomerular lesion is usually acknowledged, and it is not unlikely that the separate arterial lesions occurring in the same patient represent another similar manifestation. Although the occurrence of glomerulitis is not infrequent in cases of periarteritis nodosa, is is usually associated with concomitant arterial lesions. In such cases it is difficult to decide whether the glomerulitis is a separate toxic injury or a secondary change due to the arterial alteration.

Fundus changes in periarteritis nodosa have been noted many times and are usually reported as "albuminuric retinitis." [31] It is not known whether these changes are due to renal injury or to the toxin that produces the vascular lesion. The ophthalmoscopic picture in our patient

28. Thayer, W. S.: Johns Hopkins Hosp. Rep. **22**:1, 1926.

29. Libman, E.: M. Clin. North America **1**:581, 1917.

30. Baehr, G.: Tr. A. Am. Physicians **46**:87, 1931.

31. Baehr, G., and Manges, M.: Am. J. M. Sc. **162**:162, 1921.

was not unlike that of malignant hypertensive neuroretinitis showing papilledema, narrowed arterioles and small hemorrhages. The changes in the choroid were not visible. It is unusual to observe papilledema in Bright's disease unless there is hypertension associated with severe renal arteriolar alterations.[32] We found the renal vessels entirely normal. It is remotely possible that the retinal picture was due to the adjacent profound changes in the choroid vessels, as has already been suggested by von Herrenschwand in a similar case.[33] Falconer [34] called attention to the frequency of papillitis in bacterial endocarditis, and retinal hemorrhages are not an infrequent finding during the same condition.[35]

P. Müller [36] described characteristic changes in the retinal arterioles in his case of periarteritis nodosa. There were no accompanying illustrations. Christeller [37] mentioned arterial changes in the choroid in one of his cases, and was cognizant of the fact that such changes had not previously been described. He likewise did not include any illustration. This deficiency was subsequently pointed out by J. Böck [38] in 1929, who presented a well illustrated case showing characteristic lesions about one of the extra-ocular muscles and within the ciliary arteries. The choroid coat and retina were free. The results of the ophthalmoscopic examination had been normal. During the same year von Herrenschwand [33] demonstrated severe changes in the ciliary arteries and only scanty, atypical alterations in the choroid coat; the choroid vessels were relatively uninvolved. He attributed the changes in the choroid to the same circulating toxin that produced the changes in the ciliary arteries and did not consider them as secondary to the more profound changes in those vessels. He reported his as the first histologic study of an eye in this disease. A third report of the ocular lesions, also during 1929, was that of Goldstein and Wexler.[39] The vascular lesions in their case were confined to the choroid arteries. It is of particular importance that their case evidently showed fairly typical arterial lesions in other organs and was considered a case of periarteritis nodosa. The changes in the choroid arteries in their specimen showed histologic features almost identical with those in our case, in which the arterial lesion was an isolated occurrence.

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32. Fishberg, A. M., and Oppenheimer, B. S.: Arch. Int. Med. **46**:901, 1930.

33. von Herrenschwand, F.: Klin. Monatsbl. f. Augenh. **83**:419, 1929.

34. Falconer, A. W.: Quart. J. Med. **8**:106, 1909.

35. Litten, M.: Deutsche med. Wchnschr. **28**:37, 1902. Doherty, W. B., and Trubek, M.: J. A. M. A. **97**:308, 1931.

36. Müller, P.: Festschrift zur Feier des fünfzigjährigen Bestehens des Stadtkrankenhauses zu Dresden-Friedrichstadt, Dresden, W. Baensch, 1889, p. 458.

37. Christeller, E.: Arch. f. Verdauungskr. **37**:249, 1926.

38. Böck, J.: Ztschr. f. Augenh. **69**:225, 1929.

39. Goldstein, I., and Wexler, D.: Arch. Ophth. **2**:288, 1929.

Testicular lesions are not rare. According to Wohlwill [2] the spermatic artery is not uncommonly involved in periarteritis nodosa, but infarctions are rare. Only six such cases have been described, occurring probably because of the simultaneous involvement of the anastomosing branches from the arteria deferentialis.

The microscopic identification of unsuspected cases is no longer considered exceptional. In such instances, after histologic diagnosis, it is usually too late to obtain more tissue, and important structures, such as the eye, nerves or muscles, are not available for study. We were fortunate in obtaining those organs in which the lesion was present, but we are ignorant of possible changes in skeletal muscles or nerves.

The occurrence of isolated lesions has been reported, and typical lesions have been found in the arteries of a single organ.[40] Successive authors (Longcope,[14] Gruber [18]) have reiterated the importance of taking numerous specimens from many tissues, often cut in serial sections. The obvious case, with visible nodules or infarctions, offers no difficulty in identification of the disease at a time when gross material is available. In those cases that come to light only microscopically there is frequently a lack of sufficient material for complete study.

Gruber [18] has said: "One would think that over a hundred descriptions should be sufficient to permit identification of a disease. The microscopic picture is fairly well assured; the clinical differentiation, difficult." Two years before, Wohlwill [2] had remarked: "Each new case often presents an additional or unusual finding which adds to the composite picture or opens a new approach, and eventually may throw some light on the pathogenesis and etiology of this disease." It is with this in mind that subsequent cases may become of additional importance. The literature now abounds with excellent critical reviews accompanying reports of single cases or groups of cases.

SUMMARY AND CONCLUSION

In a case of subacute glomerulonephritis of ten weeks' duration, death occurred from uremia with pericarditis. The onset of this illness occurred eight weeks after a gonococcic urethritis complicated by a gonococcic ophthalmia. At necropsy, a right-sided subacute gonococcic endocarditis of the pulmonic valve and a typical subacute glomerulonephritis were found.

In addition, isolated necrotizing inflammatory lesions of the small arteries were found in two widely separated regions of the body, namely, the choroid coat of the eye and the testis. These vascular lesions exhibited many of the morphologic features described in periarteritis

40. Brasser, A.: München. med. Wchnschr. **33**:1126, 1924.

nodosa and were considered as belonging to that group. The larger arteries of the body were not involved, and the distribution of the lesions was not extensive enough to produce clinical manifestations The renal lesion represented a severe reaction of a sensitive organ to the toxin produced by the gonococci growing on the pulmonic valve. The vascular lesions, which in this case were anatomically dissociated from the kidney, were also considered a specific reaction of sensitive vessels to this same toxin.

The findings strengthen the conception that these vascular lesions and those of periarteritis nodosa do not represent a specific disease, but rather a specific reaction of the blood vessels to any of a whole group of variable toxins.

PERSISTENT TRUNCUS ARTERIOSUS AND CONGENITAL ABSENCE OF ONE KIDNEY WITH OTHER DEVELOPMENTAL DEFECTS

DONALD C. BEAVER, M.D.
ROCHESTER, MINN.

The anomalies in this case were: (1) persistent truncus arteriosus (common arterial trunk with complete defect of the aortic septum and partial defect of the interventricular septum); (2) aplasia (agenesia) of the left kidney and ureter; (3) accessory pancreas in the duodenum and in the ileum and (4) accessory spleen in the pancreas.

HISTORY OF CASE

A boy was delivered normally at term. The father and mother and three other children were living and normal. After the child's birth, difficulty was experienced in establishing respiration. Cyanosis became pronounced. An excessive quantity of clear mucus was present in the mouth and pharynx. No visible malformations of the external body form were present. The color continued alternately cyanotic and normal. Sleep was frequently disturbed by attacks of cyanosis, which were accompanied by rapid, irregular respirations with expulsion of thick, clear mucoid material from the mouth and nose. The pulmonary fields revealed only the presence of coarse rhonchi. The cardiac sounds were exaggerated in intensity, but murmurs were not elicited. The child died seven days after birth, following a two hour period of persistent cyanosis and increasing respiratory embarrassment. Necropsy was performed four hours after death.

SUMMARY OF MACROSCOPIC DATA

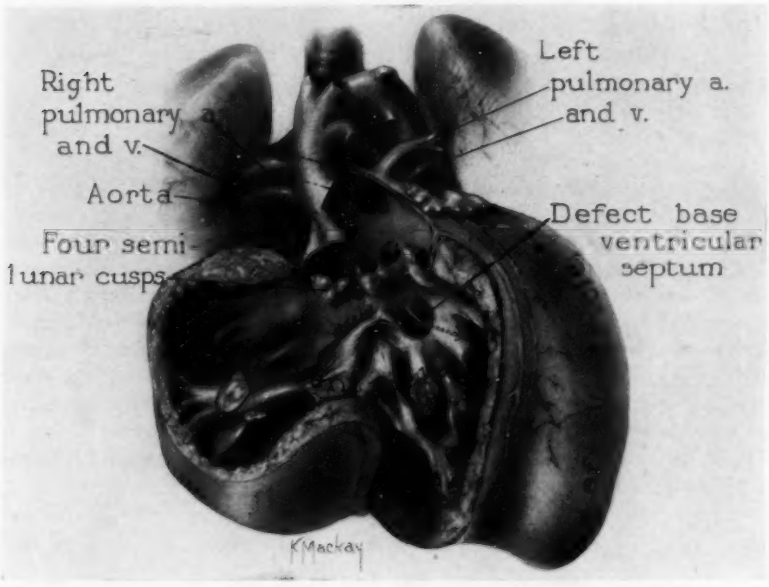
The infant was well developed and well nourished. Its length was 53 cm. (heel-vertex) and weight 3,100 Gm. Postmortem lividity was marked.

There was no free fluid in either pleural cavity. The lungs were emphysematous, and on section much frothy fluid exuded. The transverse pericardial measurement was 6 cm. The pericardial cavity contained 5 cc. of clear, yellow fluid.

The heart weighed 32 Gm. The epicardial surface was normal. The myocardium and endocardium were normal. The right auricle was dilated. The foramen ovale was closed, except for a small slitlike opening on its anterosuperior margin. The tricuspid valve was normal and measured 4 cm. in circumference. The right ventricle disclosed only moderate hypertrophy of the musculature, with dilatation of the chamber. The left auricle was normal, with normal development of the pulmonary veins. The mitral valve was normal and measured 3.5 cm. in circumference. The apex of the left ventricle was markedly rounded from dilatation, and there was marked flattening of the papillary muscles and columnae carneae. The interventricular septum was patent near the base of the heart, in the usual position

From the Section on Pathologic Anatomy, the Mayo Clinic.

of the membranous septum. The foramen thus formed was 0.5 cm. in diameter. There was no aortic opening from the left ventricle, the continuity of the circulation being maintained through the patency of the interventricular septum and through the existence of the common aortic and pulmonary trunk (persistent truncus arteriosus) placed in the usual position of the orifice of the pulmonary artery (fig.). This structure therefore carried a mixture of arterial blood obtained from both right and left ventricles. The orifice of this common arterial trunk was guarded by four semilunar valves, three posterior and one anterior. The posterior valves may be described as left, middle and right posterior. The anterior and right posterior valves were of equal size, whereas the middle and left posterior valves were each about half the size of either of the former. As a matter of fact, the middle and left posterior valve cusps were incompletely separated, or partially



Persistent truncus arteriosus, with patent interventricular septum.

fused, a fibrous raphe dividing the sinus behind the valve, without distinct individual separation in front. The valves were composed of rather soft, edematous tissue, with multiple small nodules present along the free edges. The right coronary artery emerged from the sinus of the right posterior valve, and the left coronary artery from the sinus of the left posterior valve. Their distribution in the heart from the point of emergence was as usually found. The valve ring measured 2.5 cm. in circumference. The pulmonary arteries arose as a single orifice in the left anterior portion of the common trunk 3 mm. above the semilunar valves and divided immediately into right and left branches. The left branch proceeded directly toward the left to enter the hilus of the left lung, and the right branch coursed posterior to the truncus to enter the hilus of the right lung. Not even a rudimentary septum suggested the primitive division of the truncus into pulmonary artery and aorta. The ductus arteriosus could not be identified. Beyond the orifice of the pulmonary artery, the truncus ascended as the aorta. The arch and

descending aorta were normal, except that no innominate artery existed on the right, the common carotid and subclavian arteries having independent ostia. Also a thyroidea ima was present as a branch from the right common carotid artery immediately above its origin.

The gastro-intestinal tract appeared to be normal, except for the presence of two small firm nodules 1 cm. in diameter, situated, one in the duodenum just above the ampulla of Vater and distinct from the minor papilla, and the other in the upper part of the ileum.

The pancreas weighed 6 Gm. and was normal except for the presence of two small accessory spleens in the tail.

The left kidney and ureter were absent. Careful search failed to reveal the existence of even vestigial structures. The right kidney weighed 22 Gm., and on section disclosed extensive formation of so-called uric acid infarcts. It was otherwise normal in appearance. The right ureter was normal. The bladder, genitalia and other organs and tissues were normal. The brain was not examined.

SUMMARY OF MICROSCOPIC DATA

Microscopic study confirmed the presence of splenic tissue in the tail of the pancreas and identified the nodules in the duodenum and ileum as bits of accessory pancreatic tissue.

The duodenal accessory pancreas was composed of normal-appearing pancreatic acini. In the section studied, only one island of Langerhans was found. Pancreatic ducts were present. The pancreatic tissue occupied the submucosa below the muscularis mucosa and completely replaced the muscular tunic. The muscle stopped abruptly at the borders of the pancreatic tissue.

The pancreatic tissue in the ileum was likewise composed of normal appearing pancreatic acini, but without islands of Langerhans. Pancreatic ducts were found. The pancreas occupied the submucosa between the muscularis mucosa and the muscular tunic. The mucosa and muscular tunic were atrophied from pressure. Muscle could be identified, as a narrow band, along the outer border, but the mucosa was entirely destroyed over the larger portion of the nodule.

COMMENT

The persistence of the truncus arteriosus as presented in this case is explained by failure of the aortic septum to develop. This abnormality is listed by Abbott [1] as very uncommon. She found only twenty-three cases recorded from a search of the literature and from other sources of study. The subject is adequately reviewed in her monograph.

In the case reported here, the common arterial trunk arose entirely from the right ventricle, in the position of the normal pulmonary artery. There was no suggestion of the formation of a rudimentary aortic septum. This is indicative of extremely early arrest in development, at a time when the primitive aorta arises entirely from the right side of a common ventricle. The presence of four semilunar cusps in the case is a further indication of the early developmental arrest.

1. Abbott, Maud E., in Osler and McCrae: Modern Medicine, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 707.

Congenital absence of one kidney is not so uncommon as has been generally held. In a recent review of the subject, Collins [2] found reports of 572 cases in the literature and added 9 authentic cases from the Mayo Clinic, not including the case presented here. His paper may be consulted for complete consideration of the subject. It is sufficient here to list the hypotheses as elaborated by Fortune, which Collins considers as offering an explanation of the anomaly. These are: 1. The metanephric bud may fail to appear in spite of a normally preceding mesonephros. 2. The metanephros may appear, but may undergo early regression. 3. The mesonephros may be imperfetly developed. 4. The pronephros may fail to develop, and therefore the mesonephros does not grow. Congenital absence of one kidney is frequently associated with other defects in development of the genito-urinary tract, but in the case reported here there were no such defects.

Aberrant or accessory pancreatic tissue in the gastro-intestinal tract has attracted attention since Warthin's [3] review of the subject in 1904. Simpson,[4] in 1927, reviewed 150 cases from the literature, and Moore,[5] in 1929, noted 155 cases. In spite of this apparent rarity, accessory pancreases probably are found frequently in routine postmortem examinations. Although statistics of the Mayo Clinic on this point are not available at present, it is not uncommon that accessory pancreatic tissue is seen in the duodenum, jejunum and upper part of the ileum. Moore holds: "The mode of origin of these congenital anomalies is either by adhesions of the main pancreatic anlage or from anomalous anlage."

I have been unable to find the association of these anomalies in any of the cases of congenital renal agenesia as reported by Collins, or in the reports of cases of persistent truncus arteriosus as reviewed by Abbott.

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2. Collins, D. C.: Ann. Surg. **95**:715, 1932.

3. Warthin, A. S.: Physician & Surg. **26**:337, 1904.

4. Simpson, W. M., in Contributions to Medical Science, Ann Arbor, Mich., George Wahr, 1927, p. 435.

5. Moore, R. A.: Am. J. Path. **5**:407, 1929.

MANUAL STRANGULATION

THOMAS A. GONZALES, M.D.
NEW YORK

Twenty-four cases of manual strangulation were collected from 3,340 homicides for a twelve year period subsequent to January, 1918. Nineteen occurred in adults of varying ages from 23 to 68 years, and five in new-born infants at full term. Of the adults, fourteen were females. The bodies were found under a variety of conditions and in various situations, i. e., rooms, hallways, cellars, etc.

In each case an investigation of the circumstances of the death was attempted when conditions were favorable. In this connection the character of the surroundings, the position and condition of the body and clothing, the presence of rigor mortis, postmortem lividity and visible injuries were recorded.

GENERAL OBSERVATIONS

External Lesions.—Varying degrees of cyanosis of the head were noted on eleven occasions. Two of the victims presented numerous closely grouped, pinhead-sized hemorrhages in the skin of the face and scalp. In approximately half the adults, the ocular blood vessels were engorged, and an occasional diffuse hemorrhage was observed under the palpebral and ocular conjunctivae.

With one exception, the distinctive cervical scratch marks and contusions were uniformly present. In the exception, a hemorrhage in the deep cervical fascia and muscles and a fracture of the hyoid bone served to establish the manner of death.

On a few occasions the configuration of the surface lesions suggested finger and thumb nail injuries, and their relative number and situation the possibility of determining which was the compressing hand (Beumer,[1] Mashka,[2] von Hofmann [3]).

Marks of violence elsewhere than on the neck were prominent, especially about the head and face, breast, arms and hands, and on the

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From the office of the Chief Medical Examiner of New York City.

1. Beumer, in Lochte, T.: Gerichtarztliche und polizeiarztliche Technik, Munich, J. F. Bergmann, 1914, p. 351.

2. Mashka, J.: Handbuch der gerichtlichen Medizin, Tubingen, H. Laupp'schen Buchhandlung, 1881, p. 631.

3. von Hofmann, E. R.: Lehrbuch der gerichtlichen Medizin, revised and edited by A. Haberda, ed. 10, Berlin, Urban & Schwarzenberg, 1923, vol. 1, pp. 673 and 674.

mucosa of the lips, tongue and mouth. Injuries to the anterior border of the tongue were observed in seven instances, in three of which the organ protruded and was caught between the teeth.

Deep Lesions.—Hemorrhages in the deeper layers of the skin, areolar tissue, fascia and muscles of the cervical region were present in the entire series. On two occasions there were tears of the anterior border of each sternocleidomastoid muscles without coincident lacerations of the skin.

Extravasations beneath the capsule or in the parenchyma of the thyroid gland occurred eight times; twice the submaxillary salivary gland presented similar lesions, and once the parotid gland was involved.

Petechial hemorrhages in the laryngeal and epiglottic mucosa were recorded on several occasions, while edema of the larynx (Lesser,[4] Strassmann [5]), an infrequent lesion in rapidly fatal compressions, was present in one case.

A noteworthy observation was the association of extensive hemorrhage under the laryngeal mucosa with injuries to the cartilages. Of the eight cases presenting these effusions, seven were accompanied by laryngeal fractures and one by an injury to the hyoid bone.

Injuries of the Larynx.—Fractures of the laryngeal cartilages were present eight times. The thyroid cartilage was involved in six cases; in three, the cricoid was also injured. Practically all the fractures of the thyroid cartilage occurred in the lateral alae, the exception showing injury of both superior coruna. The cricoid was fractured in five instances, including the three previously mentioned. Of the two remaining cases, one was accompanied by an injury to the hyoid bone. All of the injuries were situated in the thin anterior arch of the cartilage.

Injuries to the Hyoid Bone.—Fractures of the hyoid bone were observed four times. An extensive avulsion of the right thyrohyoid membrane and a fracture of the right greater horn were present on one occasion; the right greater cornu at its junction with the body on another, and a third revealed a fracture of the body. The fourth case, before mentioned in connection with cricoid injuries, presented a fracture of the left greater cornu.

Injuries to the trachea and its cartilaginous rings were not observed in the series (Martin [6]).

Trauma of the large cervical vessels, namely, ruptures of the carotid intima and injuries to the jugular vein was likewise absent. In one

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4. Lesser, A.: Atlas der gerichtlichen Medicin, Breslau, S. Schottländer, 1892, pt. 2, pp. 95 and 96.

5. Strassmann, F.: Lehrbuch der gerichtlichen Medizin, Stuttgart, Ferdinand Enke, 1895, p. 272.

6. Martin, E.: Arch. di antropol. crim. **15**:275, 1900.

instance, a hemorrhage in the right carotid sheath occurred without obvious injury to the artery or the vein.

Lesions of the vagus, its branches and the cervical sympathetic ganglions were not demonstrable.

Signs of asphyxia were present in the majority of cases, notably lividity of the head, face and finger-tips, hemorrhagic spots on the shoulder, back, chest and elsewhere, congestion of the lungs and petechial and diffuse hemorrhages beneath the pleura and pericardium and in the pulmonary parenchyma. Frothy, blood-stained fluid in the trachea and bronchi and distention of the chambers of the right side of the heart with dark fluid blood were also frequent features.

The cortical and medullary cerebral vessels and the choroid plexus were engorged on eight occasions, and areas of hemorrhage within the membranes and in the brain substance were noted in about a fourth of the cases.

The incidental lesions were moderate coronary sclerosis, advanced generalized atherosclerosis, chronic diffuse nephritis, fatty infiltration of the liver, syphilitic ulceration of the vocal cords with proctitis, tuberculous disease of the dorsal spine and bronchiectasis.

The lesions in infants closely approximated those found in adults. Common to all were the signs of asphyxia, the characteristic surface lesions and hemorrhage in the fascial planes and muscles of the cervical region. Two cases presented traumatic pulmonary emphysema, one a fractured skull, and a fourth an extensive hemorrhage in the laryngeal mucosa without injury to the cartilages or to the hyoid bone. The tongue protruded between the gums on one occasion.

Worthy of note was the infrequency of injury to the larynx or hyoid bone in infants in comparison with adults (Patenko [7]).

REPORT OF FIVE CASES

CASE 1.—A. Y., aged 36, was found lying in the hallway of a tenement house. Rigor was complete and the body cold. The mouth and nose were stained with blood.

Necropsy Abstract.—The body was that of a well nourished white woman, presenting a hematoma of the left frontal region, ecchymoses of the left eyelids and a laceration of the mucosa of the upper lip. The tongue was free and showed five vertical lacerations on the anterior border corresponding in position to the front teeth. A half-inch long, vertical, crescentic scratch mark (fig. 1), its convexity backward, was found on the right side of the neck, and on the opposite side was a series of small linear abrasions (fig. 2). The cervical fascia and muscles and the parenchyma of the left submaxillary salivary gland were infiltrated with blood, and there was a fracture of the body of the hyoid bone.

Extensive effusion in the galea aponeurotica and small scattered subdural hemorrhages were also present.

The viscera, aside from general engorgement, showed no lesions.

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7. Patenko, T.: Vrtljsschr. f. gerichtl. Med. **41**:198 and 230, 1884.

Fig. 1.—Thumb nail injury on the neck.

Fig. 2.—Grouped lesions, presumably finger marks.

An examination of the vaginal secretion failed to reveal spermatozoa. Chemical analysis disclosed a considerable quantity of ethyl alcohol in the brain.

An attempt, by a modified necropsy technic, to demonstrate distortion of the structures in the posterior pharynx was unsuccessful. The tongue was not forced into the nasopharynx, the relative positions of the uvula and epiglottis were undisturbed, and the vocal cords were not approximated.

Comment.—That the compression was applied relatively high is indicated by the situation of the surface lesions, the hemorrhage in the submaxillary gland and the fracture of the hyoid bone. The single vertical mark on the right side of the neck (fig. 1), presumably a thumb nail injury, and the grouped abrasions on the left (fig. 2) suggest a right hand compression.

CASE 2.—L. V., aged 35, was found lying on the floor of an abandoned automobile. The body was stiff and cold.

Necropsy Abstract.—The body was that of a slender woman, showing numerous abrasions on the shoulder, chin, cheeks and breasts. Some of the lesions resembled teeth marks. The characteristic surface lesions were present on both sides of the neck. There were also observed hemorrhages in the cervical muscles, left parotid gland and thyroid gland and ruptures of both sternocleidomastoid muscles. The galea aponeurotica was infiltrated, and the cerebral vessels were engorged.

The peritoneal cavity contained a small quantity of blood-stained fluid, and beneath the serosa of the transverse colon and the capsule of the left lobe of the liver were extensive extravasations. The visceral and parietal pleura presented petechial hemorrhages. The urinary bladder contained approximately 8 ounces (236 cc.) of urine. No spermatozoa were found.

A large quantity of ethyl alcohol was demonstrated chemically in the brain.

Comment.—That the surface lesions resulted from compression by two hands is strongly suggested by the paired thumb nail lesions on the left side of the neck and the grouped marks on the right. The case is an illustration of the typical signs of manual strangulation without injuries to the larynx or to the hyoid bone.

CASE 3.—L. F., aged 32, was found in a gas-filled room, lying beside her partially asphyxiated infant. A single gas fixture was broken from its fastening. Carbon monoxide poisoning was precluded by the dusky face and head and the absence of the characteristic hypostasis.

Necropsy Abstract.—The body was that of a well nourished woman, with cyanosis; the conjunctival blood vessels showed injection, and there were closely grouped, pinhead-sized hemorrhages in the skin of the scalp and face. The tongue was free, but presented two small vertical lacerations of its anterior border. On the right side of the neck were two vertically placed scratch marks, the convexity forward, and several small abrasions, all within a circumscribed area. On the nape of the neck were six scattered scratch marks, four of which were vertical, one horizontal and one diagonal. The left side of the neck was free from lesions.

Over the trapezius fold of the left shoulder were a series of small, closely grouped abrasions.

The free edge of the right thumb nail was torn, and some hemorrhage was present beneath the nail.

The right cervical muscles showed considerable hemorrhage. There were petechial hemorrhages in the pleura, larger effusions in the pulmonary parenchyma and frothy, blood-stained bronchial fluid.

The cerebral vessels were engorged and the urinary bladder contracted and empty.

Chemical tests for carbon monoxide, alcohols and narcotics were negative.

Comment.—A right hand compression from behind was indicated by the situation of the lesions on the right side of the neck and the scattered thumb nail injuries on the nape (fig. 3).

Fig. 3.—Grouped finger-tip injuries on the right side of the neck. Note the scattered petechial spots in the skin of the face from compression of the cervical veins.

CASE 4.—R. H., aged 59, was found dead in bed, and the death was reported as a natural one. Rigor was complete.

Necrosy Abstract.—The body was that of a poorly nourished man, with abrasions about the mouth and nose and a laceration involving the mucosa of the lower lip. There were several grouped scratch marks at the level of the thyroid cartilage on both sides of the neck. The right forearm and the left hand showed abrasions. The nail of the right middle finger was torn from its base. The glans penis presented small excoriations on its under-surface, and the prepuce showed an irregular-shaped, purplish discoloration.

Under the surface lesions on the neck were areas of extensive hemorrhage in the corium, left sternocleidomastoid, and sternohyoid muscles and left submaxillary gland and under the mucosa at the base of the tongue. The latter organ was free, but showed contusions on its anterior edge.

A vertical fracture of the thyroid cartilage, just to the left of the midline, was present. Surrounding this fracture, an extensive hemorrhage under the mucosa of the larynx extended to the true and false vocal cords and into the ventricle.

The relative positions of the tongue, uvula, epiglottis and vocal cords were normal.

The lungs were congested and flecked with areas of hemorrhage. The urinary bladder was contracted and empty. No spermatozoa were found in the buccal or rectal secretions.

It was impossible to express an opinion concerning the manner of compression from the bizarre conformation of the surface lesions.

CASE 5.—M. W., aged 45, was found lying on the floor of her bedroom. Rigor was complete and the body cold.

Necropsy Abstract.—The body was that of a slender woman, with blood stains about the nose and mouth, multiple contusions and abrasions of the right cheek and back of the right hand, lividity of the face, eyeballs showing injection, flamelike hemorrhages under the left ocular conjunctiva and petechial hemorrhages in the skin of the face and neck. The tongue protruded between the teeth, but was uninjured.

Vertical semilunar scratches and small oval abrasions were found on both sides of the neck. Hemorrhages in the deep tissue and in the left lobe of the thyroid gland were prominent features.

A vertical midline fracture of the cricoid cartilage and fractures of both superior cornea of the thyroid cartilage, with extensive hemorrhage under the laryngeal mucosa, about the vocal cords and in the pyriform fossa, were suggestive of more than one point of compression. In addition, subpleural hemorrhage, pulmonary congestion and the other signs of asphyxia were present.

Chemical examination demonstrated a trace of morphine. No spermatozoa were found.

A Japanese cook was suspected because of blood spots on his shirt. His insistence that they were received while cleaning a chicken was substantiated by a precipitin test.

GENERAL COMMENT

The failure to demonstrate injuries of the carotid artery agreed with the observation that transverse ruptures of the intima are unusual in manual compressions (Peterson, Haines and Webster;[8] Beumer[1]). Lesser[9] and Reuter[10] observed their occasional occurrence in deaths by hanging, while Friedberg[11] regarded hemorrhages in the walls of the carotid artery a valuable sign of manual strangulation.

The situation of the surface and deep lesions in relation to the level of compression is obvious from the foregoing descriptive cases.

8. Peterson, F.; Haines, W., and Webster, R.: Legal Medicine and Toxicology, ed. 2, Philadelphia, W. B. Saunders Company, 1923, vol. 2, p. 359.

9. Lesser, A.: Vrtljschr. f. Gerichtl. Med. **35**:237, 1881.

10. Reuter, F.: Ztschr. f. Heilk. **2**:172, 1901.

11. Friedberg, H.: Virchows Arch. f. path. Anat. **79**:409, 1880.

Fractures of the hyoid bone and the cornu superius of the thyroid cartilages were fairly constant in high compressions, whereas at the lower levels the cricoid, the lateral lamellae of the thyroid cartilage and the tracheal rings may be injured.

Combined fractures of the greater cornu of the hyoid bone and the superior horn of the thyroid cartilage, the consequence of bilateral pressure on the thyrohyoid ligaments, were not observed.

The location of hemorrhage in the deeper tissues was less dependent on the plane of compression. Circumscribed effusions in the salivary and thyroid glands (Aubry [12]), at the base of the tongue, about the

Fig. 4.—Double symmetrical fractures of the cricoid. Note the displacement of the fragments.

tonsil (Falk [13]) and elsewhere may result from stasis consequent on compression of the cervical vessels and have no relation to local pressure.

Cyanosis of the head, meningeal and cerebral hyperemia and hemorrhage in the membranes or in the brain substance were attributed by Mashka [2] to stasis in the right side of the heart and lungs, while Beumer emphasized the importance of cervical vascular compression in the production of these changes. He maintained, however, that irritation of the cervical nerve structures was more significant in the fatal outcome.

12. Aubry, P.: Ann. d'hyg. **31**:84, 1894.
13. Falk, F.: Vertljsschr. f. gerichtl. Med. **138**:280, 1883.

In the absence of signs of asphyxia and of deep-seated hemorrhage and injuries, with the presence of typical or atypical surface lesions, sudden death from stimulation of the vagus, its branches, notably the superior laryngeal nerves or the carotid sinus, must be considered.[14]

The importance of these structures was firmly established by the investigations of Falk,[15] Platzek[16] and Brouardel[17] on the effects of irritation of the tenth nerve, and by the recent experiments of Hering.[18] He determined that irritation of the carotid sinus produced, by reflex action, a fall in blood pressure and a disturbance of the cardiac rhythm, namely, extrasystoles and ventricular flutter or fibrillation (*Kammerflimmern*), and that the effect was augmented by atherosclerosis of the carotid arteries and by the administration of certain drugs (digitalis).

His conviction that precipitate shock and sudden death may result from these disturbances was supported by Lochte,[19] who reported a case of throttling characterized by absence of internal postmortem findings, particularly hemorrhage in the cervical muscles. That the latter observer appreciated the difficulty of diagnosis is evinced by his discussion of the various possibilities and by his statement, "There are evidently cases of violent suffocation presenting negative autopsy findings when the expert is unable to decide whether death resulted from effective attack on the neck or from internal causes." Lochte's further observation that three points are of importance, namely, stimulation of the sinus, compression of the carotid arteries and suffocation, is in accord with the interrelation between the effects of lesser degree of suffocation and augmented irritation of the sinus (Hering[18]).

In view of these observations, it is not unreasonable to suppose that these effects may bear an etiologic relation to some of the sudden deaths from traumas of the neck other than manual compression and throttling.

In the presence of the cardinal signs (characteristic bilateral lesions of the skin, deep-seated hemorrhage and injuries of the larynx or of the hyoid bone) no difficulty should be experienced in the diagnosis. The absence of one or more of these proportionately increases the uncertainty, and caution must be exercised in reaching a conclusion when

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14. The carotid sinus is the dilated portion of the internal carotid artery at its beginning. According to Hering, a fine plexus of nerves surrounding the sinus is connected with the stem of the glossopharyngeal nerve, and there are fine branches connecting it with the ramus pharyngeus of the vagus.

15. Falk, F.: Arch. f. exper. Path. u. Pharmakol. **7**:183, 1877.

16. Platzek: Vrtljsschr. f. gerichtl. Med. **22**:215, 1901.

17. Brouardel, P.: Ann. d'hyg. **2**:193, 1904.

18. Hering, H. E.: Die Karotissinusreflex auf Herz und Gefässe vom normalphysiologischen, pathologischen und klinischen Standpunkt, Dresden, Theodor Steinkopff, 1927, pp. 141 and 144.

19. Lochte, T.: Ztschr. f. d. ges. gerichtl. Med. **15**:419, 1930.

the surface lesions are not distinctive and when there is a variation of the other signs from type (Fog [20]). Deep-seated hemorrhages and injuries may result from other forms of blunt force applied to the neck, and the surface marks may be absent in compression with the gloved hand or when some soft material was interposed between the fingers and the neck.

Stevenson and Carling [21] were able to make a diagnosis by extensive effusions in the cervical muscles and fractures of the hyoid bone and of the thyroid and cricoid cartilages in a case presenting one small crescentic surface lesion at the level of the cricoid cartilage just to the right of the midline. The modus operandi was thought to be direct pressure.

A similar case was observed recently with bizarre surface lesions, extensive fractures (four in number) of the cricoid, flattening of the thyroid cartilage and a small laceration of the mucosa of the larynx from fractures of the right arytenoid cartilage.

The possibility of frontal pressure from an elbow or a foot was considered.

The greater liability in manual compressions to deep cervical hemorrhage (Schmidtmann [22]) and certain injuries, notably fractures of the thyroid alae, cricoid cartilage and more rarely tracheal rings, may establish the differential diagnosis from throttling by ligature, when the surface lesions are atypical (Wilhelmi [23]). Lesser [9] found but two instances of fracture of the thyroid plates and one of the cricoid cartilage in fifty hangings, and had no difficulty in demonstrating injuries to the superior horns of the thyroid cartilage and the hyoid bone. Reuter [10] also stated that injuries to the thyroid and hyoid cornu were frequent, while von Faber [24] found no injury to these structures in thirty-four suicides.

Fractures of the thyroid alae, cricoid cartilage and tracheal rings with deep hemorrhage are also significant when the body has been strung up to preclude the suspicion of murder (Wilhelmi [23]). Here the furrow from the constricting band may mask the distinctive surface lesions. However, it must be recognized that these injuries may result under certain circumstances from strangulations by low and forceful ligature, and the differentiation between an antemortem and a postmortem furrow is sometimes difficult or impossible (Lesser,[25] Schulz [26]).

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20. Fog, J.: Hospitalstid. **66**:265, 1923; abstr., J. A. M. A. **81**:618, 1923.
21. Stevenson, T., and Carling, W.: Lancet **1**:410, 1893.
22. Schmidtmann, A.: Handbuch der gerichtlichen Medizin, ed. 9, Berlin, A. Hirschwald, 1907, vol. 2, p. 298.
23. Wilhelmi, A.: Vrtljsschr. f. gerichtl. Med. **22**:280, 1901.
24. von Faber, W. E.: Deutsche Ztschr. f. d. Staatsarzneik. **8**:78, 1856.
25. Lesser, A.: Vrtljsschr. f. gerichtl. Med. **32**:219, 1880.
26. Schulz, R.: Vrtljsschr. f. gerichtl. Med. **11**:211, 1896.

Evaluation of the signs of violence elsewhere than on the neck should not be ignored (Taylor [27]). Their presence is usual in manual compressions of vigorous adults, unless the victim has been rendered unconscious by a blow or by alcohol or narcotics.

The position of the tongue between the teeth, suffusion of the eyelids, cerebral engorgement and signs of asphyxia, with or without atypical superficial discolorations of the cervical skin, although suggestive, are often too untrustworthy when deep hemorrhage and injuries are wanting. Certain types of asphyxia, viz., that accompanying alcoholism and narcotism, and convulsive seizures from various causes, epilepsy, etc., may present similar signs.

That there are no special signs in the viscera that enable one to differentiate hanging from manual compression or throttling was strongly emphasized by Liman [28] and others in the earlier literature.

Diagnostic differentiation from asphyxia by suffocation (pillows, blankets, etc.) may prove troublesome, especially when there are atypical surface lesions, and when death resulted from irritation of the cervical nerve structures.

Suffocation from noxious gases, gags or foreign bodies in the air passages and drowning should present no difficulties. The quantitative estimation of the chlorides in the blood of the right and left sides of the heart is of service in the positive diagnosis of drowning (Gettler [29]).

The assumption that bilateral compression forces the tongue into the nasopharynx, disturbs the relations of the epiglottis and uvula, and approximates the vocal cords was not substantiated in the series (Schultze [30]). Conceding their diagnostic importance in hanging and in throttling by ligature, when the constriction remains until rigor mortis is established, their persistence after release of pressure presupposes the immediate onset of rigor and a disregard for the natural elasticity of the laryngeal cartilages.

Late effects of manual compression were not observed in the series. In one case, not listed under strangulations, there were numerous abrasions and contusions on the face, neck and chest, deep cervical hemorrhage and fractures of the mandible and cricoid cartilage. A hematoma under the laryngeal mucosa with encroachment on the laryngeal orifice necessitated tracheotomy. The patient survived one and three quarters of an hour from the time she was found groaning and unable to speak.

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27. Taylor: The Principles and Practice of Medical Jurisprudence, (revised and edited by F. J. Smith), London, J. & A. Churchill, 1920, vol. 1, p. 680.

28. Liman: Vrtljsschr. f. gerichtl. Med. **8**:283, 1868.

29. Gettler, A. O.: J. A. M. A. **17**:1650, 1921.

30. Schultze, O. H.: Personal communication to the author.

Delayed deaths have been recorded by von Wagner,[31] Corley [32] and Fog.[20] Wagner reported the case of one who survived five days after a fractured cricoid, ruptured trachea, tears in the left carotid intima and hemorrhage in the wall of the right carotid followed by subcutaneous emphysema of the face and head.

Corley observed fracture of the cricoid cartilage, the three upper tracheal rings, projection of the latter in the lumen followed by ulceration, cellulitis and laryngeal edema. Death ensued several weeks after the injury. Fog's patient remained unconscious for two days, necropsy revealing a fracture of the superior horn of the thyroid cartilage.

Instances of complete recovery have been reported by Grosz [33] and Stolper.[34] The former observed the development of hemiparesis following a manual attempt at self-destruction, and the latter described two cases of laryngeal fractures in which the persons involved survived.

SUMMARY

Twenty-four cases of manual strangulation were studied with a view to correlating the postmortem lesions. They represent approximately 0.7 per cent of the total number of homicides, indicating the comparative rarity of this form of violent death. Nearly half presented injuries of the larynx or of the hyoid bone, and deep hemorrhages were observed in the entire series, contrasting with suicidal hangings, in which complete absence of these lesions was common.

The diagnostic significance of the surface lesions, deep cervical hemorrhage and injuries to the thyroid alae, cricoid cartilage and tracheal rings was stressed.

No instance of precipitate death from irritation of cervical nerves could be demonstrated, and the difficulty of diagnosis was indicated.

31. von Wagner: Zentralbl. f. Chir. **23**:362, 1883.
32. Corley, A.: Brit. M. J. **1**:715, 1887.
33. Grosz, K.: Wien. klin. Wchnschr. **9**:36, 1923.
34. Stolper, P.: Virtljsschr. f. gerichtl. Med. **27**:100, 1904.

A COMPARISON OF HYPERTROPHIC CHANGES IN THYROID

CAUSED IN DIFFERENT SPECIES BY ACID EXTRACT OF THE ANTERIOR LOBE OF THE BOVINE PITUITARY GLAND

ERIC W. THURSTON, M.D.
ST. LOUIS

Loeb and Bassett [1] and Silberberg [2] showed that repeated intraperitoneal injections of acid or alkali extract of the anterior lobe of the bovine pituitary gland produce marked hypertrophy in the thyroid glands of guinea-pigs. Loeb and Bassett also showed that the same effect was not observable in the thyroid glands of rats, there being little, if any, hypertrophy produced in this species. Aron [3] soon afterward confirmed both these findings, but used apparently only watery extract of the anterior lobe of the bovine pituitary gland. In addition, he studied later the effects of the extract on the thyroid glands of cats, dogs and rabbits.[4] According to his findings the thyroid gland of the rabbit is as susceptible to the extract as that of the guinea-pig; but in order to recognize the effects of small doses, it is necessary to use animals weighing on an average 1,500 Gm., because the thyroid glands of heavier animals often show normally signs of hyperactivity. In the cat and the dog he noted that relatively large doses were necessary to bring about a change in the thyroid gland comparable to that seen in this organ in the guinea-pig. Schockaert [5] noted hypertrophy of the thyroid glands of impuberal ducks following injections of extracts, emulsions and macerations of the anterior lobe of the bovine pituitary gland; an increase in weight of the thyroid glands corresponded to these changes.

In investigations in which they used young doves, Laraniov and Kotawa,[6] as well as Laraniov, Woitkewitsch and Nowikow,[7] showed

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From the Department of Pathology, Washington University School of Medicine.

These investigations were carried out with the aid of a grant for research in science made to Washington University by the Rockefeller Foundation.

1. Loeb, Leo, and Bassett, R. B.: Proc. Soc. Exper. Biol. & Med. **26**:860, 1929; **27**:490, 1930.
2. Silberberg, M.: Proc. Soc. Exper. Biol. & Med. **27**:166, 1929.
3. Aron, M.: Compt. rend. Soc. de biol. **102**:682, 1929; **103**:145, 1930.
4. Aron, M.: Rev. franç. d'endocrinol. **8**:472, 1930.
5. Schockaert, J. A.: Arch. internat. de pharmacodyn. et de thérapie **41**:23, 1931; Am. J. Anat. **49**:379, 1932.
6. Laraniov, W. T., and Kotawa, O.: Endokrinologie **9**:264, 1931.
7. Laraniov, W. I.; Woitkewitsch, A., and Nowikow, B.: Ztschr. f. vergl. Physiol. **14**:546, 1931.

that the height of the epithelium of the thyroid gland increased in proportion to the size of the dose of the extract of anterior lobe of the pituitary gland, and that in all cases hypertrophy of the gland resulted from the administration of this substance. Laraniov and Kotawa [6] also showed that marked hypertrophy of the acinar cells occurred in the thyroid glands of pigeons after the administration of these extracts. Likewise Riddle and Polhemus [8] found that, in immature doves, injections of pituitary extracts caused an increase in size and weight of the thyroid gland. On the other hand, Korenchevsky [9] noted the opposite effect in normal and cryptorchid rats, namely, a loss in weight.

In none of these investigations has a more detailed comparative study of the effects of extracts of the anterior lobe of the pituitary gland on the thyroid glands of different animals been made, and it was thought of interest, therefore, to make such a study. We shall summarize the results thus obtained.

PROCEDURE

Young, healthy male animals were used; only one female was used, a pigeon. The animals were kept in clean, airy cages, and the regular stock rations were fed.

The pituitary extract used was a sterile acid extract, subsequently neutralized, of fresh anterior lobes of bovine pituitary glands prepared in this laboratory according to the method described previously.[1] The extract was injected with aseptic precautions into the peritoneal cavity in all cases, except that of pigeons, in which the injections were made into the corresponding pelvic cavity.

As a standard of comparison I used the effects produced by three, five and seven consecutive injections of 1 cc. of the extract in guinea-pigs weighing approximately 200 Gm., one injection being given daily.

In the other species two, four, eight and fourteen injections of 1 cc. per 200 Gm. of body weight were given, one injection being administered daily. A dose of 1 cc. of extract is designated as a unit dose. In addition, larger as well as smaller doses were used. Thus mice, rats and pigeons received two and one-half times this dose daily for the same number of days. Two cats were given one daily injection of this larger dose on four and nine consecutive days, respectively, while a rabbit received four injections of this larger dose. As the smaller doses, one half and one quarter of the unit dose were used; these injections were given on four and nine consecutive days to animals of each of the species tested. Examinations of the thyroid glands of several untreated animals of each species were also made; these glands served as controls. The animals were killed by chloroform one day following the last injection and the thyroid glands removed and examined in fixed and stained specimens.

RESULTS

In Guinea-Pigs.—The effects in guinea-pigs of injections of acid extract of the anterior lobe of the bovine pituitary gland have been described previously by Loeb and Bassett, and my results agreed with the description given by these investigators. In brief, they consisted in an early marked hypertrophy of the acinar cells, the inner portions of which became granular, an enormous increase in mitoses reaching a maximum after three or four injections, and a remarkable softening

8. Riddle, O., and Polhemus, I.: Am. J. Physiol. **98**:121, 1931.
9. Korenchevsky, V.: Biochem. J. **24**:383, 1930.

and disappearance of the colloid. As a result of the hypertrophy and hyperplasia of the epithelium, the formation of intra-acinar papillae became frequent following four or five injections. After about seven injections, the number of mitoses was again distinctly diminished as compared with the findings at earlier periods.

In Mice.—The normal thyroid glands of the control animals showed microscopically a flat acinar epithelium with occasional areas of low cuboidal epithelium, small dark-staining nuclei in the acinar cells and absence of mitoses. However, as far as the occurrence of mitoses is concerned, I must make the reservation that I did not carry out a close systematic search for these structures, such as had previously been done by other investigators in this laboratory. It is therefore possible that a small number of isolated mitoses escaped my notice. I can therefore maintain only that absence of mitoses as established by the method of investigation described does not exclude the actual occurrence of a small number of mitoses. This reservation applies also in the case of the mice given injections, as well as in the case of some other species examined. The colloid was present in large quantity and was firm; the acini were round and were regular in both size and shape. Marginal vacuoles were seen in the colloid of a few peripheral acini.

The most noticeable initial effect of the injections consisted in a moderate increase in the height of the acinar cells. This was observable after two or four injections of both small and large doses. An increase in the size of the nuclei was apparent after four injections of small doses. In glands of animals given the unit dose two, four, six and nine times, the chromatin of the nuclei became more abundant and more condensed. Fusion of cells, giving the effect of multinucleated cells, was apparent in the glands of animals given the large doses for two, nine and fourteen days and those given the unit dose fourteen times. The thyroid gland of the animal given nine injections of the large dose showed intra-acinar papillae. No mitoses were seen in any of these thyroid glands. In every case, irrespective of whether small or large doses had been given, the colloid remained firm throughout the greater part of the gland. In only a few did the colloid in the peripheral acini show slight vacuolation about their borders; however, in the thyroid gland of the animal that had received fourteen injections of the largest dose, the colloid showed, in addition, vacuolation of the central acini. In a mouse that had received four injections of the largest dose, colloid droplets appeared in the acinar cells. This was an exceptional occurrence. Phagocytes were seen in a few acini of the thyroid gland of the animal receiving six injections of a unit dose. In a few of the mice there was a slight reduction in the amount of colloid, which was relatively most noticeable after two injections of the large dose.

Summary: Briefly, then, the effects of injections of the acid extract on the thyroid glands of the mice were quite different in intensity from those seen in the thyroid glands of the guinea-pigs which had been similarly treated. There can be no doubt that there was a response also in the thyroid glands of the mice that had received repeated injections of the extract. But this response was slight and manifested itself most noticeably in a moderate increase in the height of the acinar cells and in a moderate increase in the size of the nuclei. The pronounced increase in the height of the epithelium which was so noticeable a feature in the guinea-pigs was not seen here. Likewise, mitoses were not seen in the acinar cells of the mice given these injections. Furthermore, the marked softening and absorption of colloid noted in the thyroid glands of the guinea-pigs were not demonstrable in those of mice.

In Rats.—The control thyroid glands showed an epithelium of moderate height, on the average slightly higher than that seen in the thyroid glands of the normal guinea-pigs, and likewise higher than that seen in the thyroid glands of the normal

mice, the acinar epithelium of which was flat. However, as described by Loeb, certain differences occurred in the height of the epithelium of the peripheral and central acini in the guinea-pigs. In the rats the cytoplasm of the acinar cells was more abundant than in the guinea-pigs, but it did not readily stain with eosin. No mitoses were seen as a rule. The colloid was present in large quantity. It was firm and was vacuolated only at the borders in some peripheral acini.

After relatively few (four) injections of a small or large dose of acid extract, the epithelium began to increase in height. The cytoplasm stained now more deeply with eosin because of an increase in intracellular granules. Mitoses were seen in glands of animals that had received two or four unit doses. They were absent or very scarce in the thyroid glands of the other animals. This indicates that acid extract may exert a certain stimulating effect on the mitotic activity of acinar cells in the thyroid gland of the rat.

The colloid was reduced in amount, e. g., after four and nine injections of a small as well as of a unit dose. However, in all glands it remained firm, but underwent vacuolation in the peripheral acini after a few injections of various doses had been given. Occasionally phagocytes were seen in the colloid of a few acini.

A tendency to retrogression of the hypertrophic changes was noted in the thyroid glands of the rats given fourteen injections of the unit dose as well as in those given the larger doses. In this case, the acini were large, and the colloid was at least as abundant as in the thyroid glands of the control animals or perhaps even more so; moreover, it was hard, moderately retracted in most acini and showed vacuolation only in some peripheral acini. The epithelium was not higher, and in places was even flatter than the epithelium in the controls. It is possible that one has in this case to deal with the first stage of a phenomenon observed by Loeb and Friedman[10] in guinea-pigs, in which after long-continued injections of acid extract there gradually developed an immunity to the effects of the extract, and the gland returned to the normal state.

Summary: If the effects of the extract on the thyroid glands of the mice and the rats are compared, the latter showed slightly more marked changes. The epithelium became relatively higher, there was a greater diminution in colloid, and the mitoses were more numerous. In addition, there was the tendency in the thyroid gland of the rat to retrogression of the hypertrophy after relatively long-continued injections of the extract.

But the effects of the extract on the thyroid glands of the guinea-pigs were very much greater than those on the thyroid glands of the rats, and the thyroid reactions of the rats resembled much more those of the mice than those of the guinea-pigs. Measured by this standard there was only a relatively slight difference between the rats and the mice. This applies to the height of epithelium and the number of mitoses, as well as to the softening of the colloid. In the thyroid glands of the rats there was not the general marked softening or the absorption of the colloid seen in these glands of the guinea-pigs. There was a moderate decrease in amount, however, in the thyroid glands of the rats, with a tendency to vacuolation of the colloid especially in the peripheral acini.

In Rabbits.—The thyroid glands of the control animals showed a great amount of colloid, which was hard and slightly retracted, and in which there were peripheral vacuoles. The epithelium generally was flat or low cuboidal; the nuclei were small, and the cytoplasm was evenly stained. No mitotic figures were seen. The acini were round, regular in shape and fairly large.

10. Loeb, Leo, and Friedman, Hilda: Proc. Soc. Exper. Biol. & Med. **29**:172, 1931.

With the smallest doses repeated from four to nine times there was a moderate increase in the height and size of the epithelium. A number of mitoses appeared after four injections of the smallest dose. The colloid disappeared almost entirely. This was especially marked in the peripheral parts of the gland, where the acini contained only thin strands of colloid; but also the central acini were small, irregular and collapsed in many places. The colloid that remained here was hard and vacuolated.

After from six to fourteen injections of a unit dose there was only a moderate diminution in colloid. It remained firm in all glands, retracted and peripherally vacuolated. After six injections of a unit dose, occasional acini showed softening of the colloid. Phagocytes were not seen in any of these glands. The central acini generally became smaller and more irregular, and they had a tendency to lose their lumens as early as after four injections of a unit dose. After two injections of a unit dose, the epithelium was only slightly changed in height. With four and six injections of a unit dose, the epithelium was variable in height, the low cuboidal to columnar type being seen in different areas of the same gland. The higher cells occurred mainly in peripheral acini. After many injections of a unit dose had been given, the epithelium was generally low cuboidal. Mitoses were not seen even after a considerable number of injections of small or large doses had been given.

After four injections of a large dose, the colloid was greatly reduced in amount, only shreds being left in most glands. The acini were very irregular in size and shape, and peripheral giant acini, the result of coalescence of several smaller ones, were seen. The epithelium varied markedly in character throughout the gland, being flat or low cuboidal in some areas and columnar in others. The cytoplasm of many cells showed vacuolation.

Summary: In comparison with the effects seen in the thyroid glands of the rats and the mice, the effects in the thyroid glands of the rabbits were more pronounced; both the rabbits and the rats showed more marked changes than the mice. But as compared with the effects on the thyroid glands of the guinea-pigs, those seen in the thyroid glands of the rabbits were relatively slight. The most noticeable effects seen in rabbits occurred after only four injections of relatively very small or very large doses. These consisted mainly in a marked diminution of colloid and an increase in the height of the epithelium, but the latter varied greatly irrespective of the number of injections and was never as high as in the thyroid glands of the guinea-pigs after injections of extract. There was also a great difference in regard to the occurrence of mitoses in the thyroid glands of these two species. After a large number of injections had been given, the effects, as far as the height of epithelium, softening of the colloid and increase in number of mitoses was concerned, seemed less than after a smaller number of injections.

In Cats.—The thyroid glands of the normal cats showed a great amount of firm, deeply staining colloid, which was retracted in many acini, while in others peripheral vacuolation was seen. The epithelium was on the whole flat or low cuboidal; yet the cells were fairly large, and in one control animal granules were seen in the cytoplasm. Mitoses as well as phagocytes were not observed.

The most noticeable effect produced by injection of extract in the thyroid glands of these animals, irrespective of size and number of doses given, was a marked diminution of colloid. This effect was most pronounced after nine injections of a very large dose, and after six and nine injections of a unit dose. But in those glands in which colloid remained, it was firm, retracted and often contained peripheral vacuoles. Phagocytes appeared in the colloid in a certain number of cases. After four injections of extract, the cells tended to become wider and the

cytoplasm clear and slightly vacuolated; the increase in the height of the epithelium, while definite after four injections of the small dose, was not yet great; only after six or more injections of a unit or large dose had been given, did the acinar epithelium assume columnar size throughout the whole gland. Mitoses appeared only in relatively small numbers, and this occurred after four injections even of small doses. The maximum increase observed did not exceed two mitoses per section. As a result of the absorption of the colloid the acini became smaller and more irregular, and the lumen in some cases disappeared, so that slits developed after repeated injections of the extract. Intra-acinar papillae were also seen after as many as nine injections.

Summary: In comparison with the effects on the thyroid glands of the mice and the rats, the effects on the thyroid glands of the cats were more marked. The changes were quite similar in many respects to those seen in the thyroid glands of the rabbits. Both showed reduction in the amount of colloid, increase in the height of the epithelium after repeated injections and only slight increase in the number of mitoses. Intra-acinar papillae appeared only after a relatively larger number of injections. Neither the rabbits nor the cats showed marked softening of the colloid, and the acini generally remained large and fairly regular after the first injections. Later the colloid disappeared without apparently undergoing the processes of liquefaction that often were so prominent in the thyroid glands of the guinea-pig, after injections of extract.

The thyroid glands of the cats did not show the marked increase in the height of the epithelium nor the marked softening of the colloid that was seen in the thyroid glands of the guinea-pigs at a very early stage of the injection nor were mitotic figures as numerous.

In Pigeons.—The control thyroid glands of the normal pigeons contained moderate amounts of colloid, which was firm, slightly retracted and vacuolated in some of the peripheral acini. The epithelium was flat or very low cuboidal. Mitoses were not noted nor were lymphocytes seen.

In the thyroid glands examined after four injections of one quarter or one half of a unit dose there was a moderate increase in the amount of colloid. The colloid was firm, but vacuolated in the peripheral acini, and the acini were round and regular. Masses of lymphocytes were seen throughout the sections. The epithelium was somewhat irregular as to height, but in general varied from high cuboidal to columnar in shape. Mitotic figures were numerous. Phagocytes were occasionally seen in the colloid.

After nine injections of a quarter or of a half of a unit dose there was a marked reduction in the amount of colloid. The colloid that remained was vacuolated and retracted. The height of the epithelium was increased and a greater number of papillae and lymphocytes were noted; also, mitoses were numerous. The cytoplasm of the cells did not become vacuolated as it did with larger doses of extract.

With a unit dose given two or four times there was a moderate reduction in colloid. There was also an increase in the height of the epithelium, which in some cases became columnar. The acini were reduced in size, especially in the central portions, where only small round acini or slits were found. Intra-acinar papillae were numerous, and lymphocytes were found in the subcapsular tissue; they infiltrated also many of the interacinar spaces. No mitoses were seen after two injections, and only a few after four had been received. There was a tendency to vacuolation of the cytoplasm of the acinar epithelium in both series.

After six, nine and thirteen injections of a unit dose there was a moderate reduction in colloid, which was most marked after thirteen injections. Intra-acinar

papillae were noted in all three thyroid glands. Lymphocytes were not seen after six injections, but were present after nine and thirteen injections. The epithelium was high cuboidal after six and nine injections and was high columnar after thirteen. The cytoplasm of the acinar cells was usually somewhat vacuolated. Mitoses were absent in all three specimens. Phagocytes were seen in a few acini after both six and thirteen injections.

In two pigeons in which two and one-half times the unit dose had been given four times, there was a moderate reduction in the colloid. That which remained was firm and retracted and showed small-sized peripheral vacuoles in many of the acini. The acini were irregular in both specimens. They contained intra-acinar papillae. The epithelium, the cytoplasm of which was vacuolated, was high cuboidal after two injections and reached columnar size after four. A few mitoses and a few lymphocytes were seen after four injections; they were lacking after two injections.

In the thyroid glands of pigeons that had received six, nine or fourteen injections of two and one-half times the unit dose, the colloid showed moderate reduction after six and nine injections but a greater reduction after fourteen injections. In all three specimens, that which remained was vacuolated. The acini were small and round or reduced to slits. The epithelium was generally high cuboidal, and the cytoplasm of the acinar cells vacuolated. Mitoses were not seen. In all three specimens, masses of lymphocytes were noted in the interacinar spaces.

Summary: The effects of injections of acid extract of the anterior lobe of the bovine pituitary gland on the thyroid glands of the pigeons varied somewhat with the size and number of doses. With a very small dose injected four times there was an increase in the amount of colloid in the gland; the mitoses became numerous and the epithelium higher. With small doses repeated nine times or a larger dose given from two to fourteen times the colloid was reduced in amount. The height of the epithelium increased with the size of the dose and the number of times it was administered. Mitoses were much increased after small doses had been given; after larger amounts of extract the mitoses became much more infrequent. If more than four injections were given, intra-acinar papillae appeared. Masses of lymphocytes were also seen between the acini or beneath the capsule, after four or more injections, irrespective of the dose.

The effects were more marked and persisted for a greater length of time than those seen in the thyroid glands of the mice, rats, rabbits or cats. In certain respects, the changes were very similar to those observed in the thyroid glands of the guinea-pigs. These resemblances concerned chiefly the great increase in the number of mitoses and in the height of the epithelium. However, the marked softening of colloid seen in the thyroid glands of the guinea-pigs was not noticeable in the pigeons.

COMMENT AND CONCLUSIONS

These investigations show that injections of acid extract of the anterior lobe of the bovine pituitary gland affect the thyroid glands of different species of animals in principle in the same way, but that the effects differ in intensity. In regard to the intensity of the changes produced, the species studied can be arranged in the following order, beginning with the species that showed the least effects of the injections: (1) mouse, (2) rat, (3) rabbit, (4) cat, (5) pigeon and (6) guinea-pig. My results differ from those of Aron, who concluded that the thyroid gland of the cat and that of the rabbit are as susceptible to the action of

the extract as that of the guinea-pig. I find that the thyroid gland of the latter species is much more responsive to these extracts than that of the rabbit or that of the cat. Furthermore, Aron attributed the lack of effects observed in the thyroid gland of the rat to the greater activity of the normal gland in this species. However, my findings, according to which even very large doses call forth only every slight reactions of the thyroid gland of the rat, make it probable that the latter is little responsive to these extracts, and make it doubtful that this state of normally greater activity in the thyroid gland of the rat is responsible for the relative lack of reaction to the injections, and that the greater height of the acinar epithelium observed in the normal thyroid gland of the rat as compared with that in the normal guinea-pig indicates a reaction to hormone of the anterior lobe of the pituitary gland. Moreover, in comparing the thyroid glands of the normal rat and guinea-pig one must consider the fact that the latter usually shows a considerable difference in the structure of the peripheral and central areas of the same gland, and that in the center the acinar epithelium may be relatively high. Furthermore, the proliferative activity of the thyroid gland of the guinea-pig is normally at least as great as that of the rat, as shown by Rabinovitch. It is furthermore of interest to note that the rat's thyroid gland which is so little responsive to stimulation by extract of the anterior lobe of the pituitary gland, is very responsive to the stimulating effects of iodine, as shown by Irsigler and especially by the quantitative investigations of Rabinovitch.

My investigations confirm thus the observations of Loeb and Bassett, who showed that injections of extract of the anterior lobe of the bovine pituitary gland exert a very slight effect on the thyroid gland of the rat. These results make understandable also why the marked increase in weight that takes place in the thyroid gland of the guinea-pig under the influence of these extracts is lacking in the rat, but it is not clear why there should be an actual decrease in weight in the thyroid gland of the rat, which, according to Korenchevsky, takes place after injections of these extracts. As far as the effects of the extracts on the thyroid glands of birds are concerned, my investigations, in principle, are in accordance with those of Schockaert, who noted a marked hypertrophy of the acinar cells and a marked decrease in the amount of colloid in young ducks under the influence of massive doses of extract of the anterior lobe of the bovine pituitary gland. However, in the pigeon, I observed only a moderate reduction in the amount of colloid. Both Schockaert and I observed the appearance of lymphocytes in the interacinar spaces of the thyroid glands of birds which had been made experimentally hypertrophic. This phenomenon was not observed by me in the thyroid glands of other species; it corresponds to the especially marked activity of lymphocytes observed by Loeb and Addison

following transplantation of strange tissues in birds, and is evidently related to the greater number of lymphocytes circulating in the blood of birds than in that of mammals. This finding is also of interest in connection with the accumulations of lymphocytes that are found in the human thyroid gland in exophthalmic goiter. My observations on the thyroid gland in pigeons harmonize also with the findings of Riddle and Polhemus and of Schockaert, who found an increase in weight in the thyroid glands of birds under the influence of these extracts. According to Laraniov, Woitkewitsch and Nowikow, the height of the acinar epithelium increases the more the greater the dose of the extract that is injected.

If the present series of investigations is now considered as a whole, certain facts are noted:

1. There is a pronounced difference in the reactivity of thyroid glands.

2. On the whole, a parallelism exists in the intensity of the different kinds of effects exerted by extract of the anterior lobe of the bovine pituitary gland. Thus, in the mouse, all effects are almost lacking. There is a very slight increase in the size of the epithelium, with only very slight, if any, reduction in the amount of colloid as indicated by an increase in the size of the vacuoles in the periphery of the colloid; there is no definite increase in mitoses. In the rat, the effects are similar to those in the mouse, but there is here a slight increase in mitotic activity. The height of the epithelium is slightly more increased than in the mouse, and while no real reduction in the amount of colloid takes place and the latter substance remains firm, there is greater vacuolization in the periphery of the colloid. In the rabbit and the cat, a much more marked reduction in the amount of colloid is present than in the mouse and the rat; there are also an increase in the height of the epithelium and an increase in the number of mitoses or a new appearance of mitoses under the influence of the injections. In this species, the lumens of the acini may almost disappear, slits may develop, and the character of the acini may become irregular; in the rabbit, furthermore, coalescence was observed in some of the peripheral acini, while in the cat some intra-acinar papillae appeared. In addition, there was in the rabbit occasionally perhaps a slight indication of the softening of colloid in a few acini. In birds, the increase in the number of mitoses was greater than in the species just discussed. The increase in the size of the epithelium was also more considerable and the intensity of absorption of colloid greater, especially when smaller doses of acid extract were administered; the character of the acini was more irregular, slits and intra-acinar papillae appearing more commonly. In the guinea-pig, the increase in the height and size of the epithelium, the increase in the number of mitoses, the solution and absorption of colloid and the resulting irregularity of acini were most pronounced.

3. The thyroid gland of the guinea-pig differs from the others in that in the former alone marked liquefaction of colloid within the acini can be observed; the absorption of colloid may lag behind in this case. In the other species, liquefaction apparently takes place more slowly, so that the absorption of the liquefied colloid can keep pace with the process of liquefaction, and the colloid remaining in the acini is still rather solid. It was this rapid solution observed by Loeb in the guinea-pig which suggested the possible significance of enzymes in this process, and which led to the differentiation of two processes of absorption of colloid in the thyroid gland, (*a*) the process of diffuse solution and (*b*) the process of localized solution by means of phagocytes, the latter being especially pronounced, as Rabinovitch observed, in the thyroid glands of guinea-pigs following administration of potassium iodide.

4. While in general an increase in the number and size of doses causes an increase in the intensity of the resulting hypertrophy and hyperplasia of the thyroid gland, under certain conditions it has been found that if the amount of extract of anterior lobe of the pituitary gland administered or the length of time during which injections of the extract are made exceeds a certain limit a reverse effect takes place: the hypertrophy diminishes. This corresponds to the observation of Loeb and Bassett that a relative decrease in the number of mitoses takes place following the first days of injection during which the maximum of proliferative activity has been reached. The process of retrogression was studied still further by Loeb and Friedman in the guinea-pig, and a corresponding process was also observed in birds by Schockaert. I noted indications of analogous phenomena in various species. Thus in the rat the height of the acinar epithelium decreased again after many large doses had been given; this was apparently due to pressure exerted by the colloid, which must have increased in amount under these conditions. In the rabbit, after a larger number of unit doses had been given, mitotic activity, which had been noticeably increased under the influence of smaller doses, disappeared again. Smaller doses seemed likewise to be more effective in causing disappearance of colloid than larger doses. In the pigeon, also, smaller doses of extract seemed to stimulate the proliferative activity and the reduction in the amount of colloid more than did larger doses. Furthermore a small number of injections of small doses of extract seemed to cause an increase in the amount of colloid in the acini in this species. The first effect in this case consisted therefore apparently in a stimulation of the process of colloid production.

SUMMARY

A comparative study has been made of the effects of injections of acid extract of the anterior lobe of the bovine pituitary gland on the thyroid glands of a number of species of animals. The effects of the

acid extract are in principle the same in all species investigated, but they differ much in intensity in the different species. In regard to the intensity of the changes observed, the species studied can be arranged in the following order: (1) mouse, (2) rat, (3) rabbit, (4) cat, (5) pigeon and (6) guinea-pig, the mouse showing the least and the guinea-pig the greatest effects of the injections.

There is, on the whole, a parallelism in the effects of the extract—the hypertrophy of acinar epithelium, the proliferative activity as indicated by the number of mitoses, the absorption of colloid and the change in the size and shape of acini. However, in some species certain peculiarities can be noted that are lacking in others. I mention in this respect the accumulations of lymphocytes taking place in the thyroid gland of the pigeon under the influence of the extract.

The effect of the extract on the thyroid gland of the guinea-pig differs from that in all the other species through the liquefaction of colloid, which in the former species may be so marked that the absorption lags behind the process of liquefaction, while in other species liquefaction takes place so slowly that, in general, absorption can keep pace with the processes of solution.

After the administration of larger doses, especially if they are given during a longer peroid of time, a retrogression of certain effects of stimulation may occur in various species of animals.

PRIMARY EPITHELIAL TUMORS OF THE VERMIFORM APPENDIX

OBSERVATIONS BY SILVER IMPREGNATION

GEORGE VAN S. SMITH, M.D.
BROOKLINE, MASS.

A review of the pathologic records of the Free Hospital for Women covering the period from October, 1902, to January, 1932, disclosed twenty-two cases of primary epithelial neoplasm of the vermiform appendix. Twenty-one of these tumors belonged to the class commonly described as carcinoid. The other was a true malignant columnar cell adenocarcinoma such as is characteristic of other portions of the large intestine. During this same period 7,865 appendixes removed at operation were examined grossly and microscopically. The conditions found were classified as follows:

Miscellaneous (mucocele, concretion, cyst)	13
Normal condition	3,232
Dilated appendix	537
Obliterated appendix	1,021
Chronic appendicitis	2,467
Periappendicitis	374
Acute appendicitis	71
Subacute appendicitis	114
Tuberculous appendicitis	9
Endometrioma of appendix	1
Carcinoid tumor of appendix	21
Carcinoma of appendix (primary, 1; metastatic, 4)	5
Total	7,865

The occurrence of carcinoid tumors in this clinic, then, is 1 to every 375 appendectomies, or 0.26 per cent. Primary carcinoma of the appendix is obviously extremely rare.

In 1906, Rolleston and Jones [1] published a complete historical summary on these tumors and, after carefully analyzing the literature, concluded that forty-two of the reported tumors could be accepted as authentic. Of this total, thirty-three had been removed during life, all being entirely unsuspected. Five of the forty-two were considered to be similar to the usual adenocarcinoma of the large intestine.

From the Pathological Laboratory, Free Hospital for Women.

1. Rolleston, H. D., and Jones, L.: Am. J. M. Sc. **131**:951, 1906.

Forbus,[2] in 1925, made another complete survey and included the more recent studies, done chiefly by Masson by the use of silver impregnation methods, on the relation of the carcinoid tumors to the chromaffin tissues of paraganglions and of the suprarenal medulla. From his own studies he favored the view that these were of endocrine origin, being derived from the chromaffin cells of the crypts of Lieberkühn, which have the peculiar ability to precipitate silver from a solution of silver nitrate and hence are called argentaffin. Since the carcinoid tumors have this same ability, they are also called argentaffin. He quoted Jackson to the effect that 317 of these tumors of the appendix had been reported up to 1923.

Of the twenty-one appendixes with carcinoids now being reported, twenty showed the disease located in the distal third, either as a nodular swelling or as an induration, without any change in caliber or even with a tapering-off. The other appendix contained a firm, round tumor, 1.5 cm. in diameter, in its base, its lumen being obliterated throughout. In fourteen, the lumen was obliterated proximally; in the other six, the disease was found either projecting backward up the lumen in a polypoid fashion or simply filling it at the point of growth. Nine of the appendixes at operation were found adherent to surrounding structures to a greater or less degree. In no case was metastasis observed.

Microscopically, in every case the characteristic picture was that of small round or oval masses of epithelial cells (with a suggestion of adenomatous formation), which varied moderately in size, but which showed only slight pleomorphism, very rare mitoses and no hyperchromatism, i. e., very low, if any, malignancy. Five of the appendixes showed no invasion by the tumor beyond the lumen and submucosa; in three the muscularis was involved; eight showed invasion to the serosa, and in five the mesentery contained nests of cells. In every instance chronic inflammation was evident by increase of connective tissue and by diffuse or focal infiltration of round cells in the muscularis and serosa.

Nine of the patients were between the ages of 23 and 29; the remaining twelve were between 33 and 59. Eight of the patients have been untraceable since operation. Five of the others were well over ten years after operation. The remaining eight were well from six months to seven years later. Only three had complained of symptoms that could be interpreted as referable to the appendix.

In addition to the routine gross and microscopic examination of these tumors and appendixes, sections were impregnated with silver

2. Forbus, W. D.: Bull. Johns Hopkins Hosp. **37**:130, 1925.

(Sara Danziger) by a modification of Hasegawa's silver nitrate method [3] as follows:

1. Celloidin sections of tissue fixed in alcohol-formaldehyde were cut from 14 to 16 microns thick.

2. After being thoroughly washed in distilled water, they were left over night in a 2 per cent silver nitrate solution.

3. They were then washed again in distilled water and left for from six to eight hours in an ammoniacal silver solution made thus: To 10 cc. of 1 per cent silver nitrate is added 1 drop of 40 per cent sodium hydroxide; the precipitate that forms is nearly dissolved by 4 or 5 drops of strong ammonium hydroxide; distilled water is added to make a volume of 50 cc.

4. After being washed for a few minutes in distilled water, the sections were run through 95 per cent alcohol, oil of origanum and xylene and mounted in xylene-balsam.

It was possible to examine silver-impregnated sections of sixteen of the twenty-one carcinoids. All showed the characteristic granules of reduced silver—despite the fact that they had been preserved in formaldehyde for from six months to seventeen years from the time of operation. It was also possible to study the argentaffin cells of the appendixes themselves in seventeen of the cases. The lumens of three were completely obliterated, and sections showed no silver-reducing cells. Of the eight appendixes the lumens of which were obliterated only just proximal to the tumor, four contained no argentaffin cells in the sections that were cut (away from the point of obliteration); sections of the other four (from 14 to 16 microns thick) contained 1, 23, 30 and 36 argentaffin cells, respectively. The lumens of the remaining six were not obliterated—sections of two showed no argentaffin cells; 26, 40, 50 and 100 cells, respectively, were counted in the sections of the others. A comparison of the ages of the seventeen patients from whom these appendixes were removed with the number of silver-reducing cells in the sections suggests that the number of these cells decreases with increasing years. Thus eight of the nine patients who showed no argentaffin cells except in the carcinoids were 35 years of age or older, the other being 23. Of the eight patients who showed argentaffin cells, five were under 35.

The twenty-second tumor in this series was a true adenocarcinoma, located entirely within the appendix of a woman who was 41 years old at the time of operation (Dr. W. P. Graves) and is now well four and one-half years later. She had had pain in the right lower quadrant of the abdomen for from five to six years and that region was tender to palpation before operation. The appendix was found enlarged, congested and adherent to the right tube and ovary. It was 5.3 cm. long and 2 cm. in diameter. On section, the lumen was dilated, full of mucus

3. Hasegawa, T.: Virchows Arch. f. path. Anat. **244**:8, 1923.

and lined with irregular small papillary excrescences. No normal mucosa could be found. Microscopically there was no invasion beyond the submucosa. Impregnation with silver disclosed no argentaffin cells.

It was felt to be worth while to investigate the argentaffin cells in appendixes that were removed in the routine, in relation to the age of the patient, the symptoms and the pathologic observations. Accordingly, from March 1, 1927, to Feb. 8, 1929, sections of 261 appendixes were impregnated with silver according to the method described in addition to being subjected to the usual pathologic study. Since most often the argentaffin cells in only one section were counted, it is obvious that merely a rough index could be obtained. For example, in a few instances the lumen of the distal portion of the appendix was obliterated, and in this area no argentaffin cells were seen, whereas a section taken from a proximal portion showed these cells. Usually, however, multiple sections were likely to give fairly similar counts.

Twenty-nine appendixes were described as normal. Sections of five gave an argentaffin cell count of 0; sections of six gave counts between 100 and 200; sections of the remainder, from 10 to 70. It was impossible to correlate age, symptoms and cell count.

No argentaffin cells were seen in a section of an acutely inflamed appendix.

Of twelve appendixes with subacute inflammation, four contained no cells; one contained over 100 cells; the other seven showed from 10 to 50. No correlation could be made between age and cell count. Eleven of the patients from whom these appendixes were taken had had symptoms pointing to appendicitis.

One hundred and sixty appendixes showed evidence of chronic inflammation. In thirty-nine no argentaffin cells were seen. Less than 20 cells were counted in forty-four. The rest gave counts from 21 to 172. One hundred and eight appendixes in this group gave cell counts of 40 or less; sixty-seven came from patients between the ages of 20 and 40. It is interesting that twenty-three of these sixty-seven patients had symptoms suggesting a disturbance of the appendix, whereas only ten of the remaining ninety-three had symptoms. That this is not a coincidence is suggested by the fact that thirty-four of these ninety-three patients were between the ages of 20 and 40, and yet only two had symptoms indicating possible appendical upset. Fifty-one appendixes in this group came from patients over 40 years of age. Thirty-five of these gave counts of 40 or less. On the other hand, of the fifty-two appendixes with counts of 40 or more, thirty-seven were from patients under 40. From studying this group, then, the impression is conveyed that the argentaffin counts are less both in appendixes from older patients and in those with sufficient inflammation to give symptoms.

Silver-impregnated sections of fifty-nine appendixes having obliterated lumens failed to show any argentaffin cells. Twenty-eight of the patients were less than 40 years old; thirty-one were over 40; fifty-four were over 30. (One hundred and one in the group with chronic appendicitis were over 30 and fifty-nine under 30.) Only seven of this group had symptoms suggesting appendicitis, and four of these were under 40.

SUMMARY AND CONCLUSIONS

The incidence of primary epithelial tumor of the appendix encountered at this clinic is 0.27 per cent.

Twenty-one carcinoids have been briefly described in relation to clinical and pathologic findings and argentaffin characteristics which link these tumors up with the argentaffin cells of the appendix.

One primary columnar cell adenocarcinoma of the appendix has been described. It did not reduce silver. Incidentally, another appendix contained metastatic squamous carcinoma of the cervix which did not reduce silver.

From a study of the argentaffin cells of 261 appendixes the following statements seem justified: Regardless of the age of the patients, the symptoms and the amount of inflammation, the number of argentaffin cells varies considerably. In general, however, the number of these cells decreases with age and inflammation, especially if symptoms are present.

General Review

PAGET'S DISEASE OF BONE

HENRY L. JAFFE, M.D.
Pathologist, Hospital for Joint Diseases
NEW YORK

In 1877, Sir James Paget described the advanced clinical form of the bone disease which now bears his name.[1] The existence of the disease had been recorded prior to Paget's publication. Wraný's case of "spongy hyperostosis" and Wilks' case of "osteoporosis, or spongy hypertrophy of the bones" (which was among the 5 recorded in Paget's original paper) testify to this fact.[2] Both Wraný and Wilks deserve credit along with Paget for the recognition of the advanced clinical form, but Paget's original paper will remain a monument to his great clinical and scientific skill. To his lucid description of the advanced clinical form of this disease little has been added, and after his other papers[3] the condition was acknowledged by many observers as a distinct entity.

However, much confusion was introduced with von Recklinghausen's description of generalized osteitis fibrosa cystica, especially since he believed that the diseases described by Paget and himself were anatomically closely related.[4] Nevertheless von Recklinghausen tried to differentiate them histologically, recognizing that in Paget's disease there was a greater degree of new bone formation than in generalized osteitis fibrosa cystica. Soon afterward, the majority of German pathologists postulated an intimate relationship between these diseases. Christeller, in 1923, developed this erroneous view to its last conception when he classed them as "hyperostotic and hypostotic" forms, respectively, of fibrous osteodystrophy.[5] Nevertheless, many clinicians, radiologists and pathologists disagreed with this point of view.

From the Laboratory Division, Hospital for Joint Diseases.

1. Paget, J.: Tr. Roy. Med. & Chir. Soc. London **60**:37, 1877.

2. (*a*) Wraný, quoted by Paget.[1] (*b*) Wilks, S.: Tr. Path. Soc. London **20**:273, 1869; Lancet **2**:1627, 1909.

3. Paget, J.: Tr. Roy. Med. & Chir. Soc. London **65**:225, 1882; Illust. M. News **2**:181, 1889.

4. von Recklinghausen, F.: Festschrift, Rudolf Virchow zu seinem 71. Geburtstage, Berlin, G. Reimer, 1891.

5. Christeller, E.: Ergebn. d. allg. Path. u. path. Anat. **20**:1 (Pt. 2) 1923.

The complete separation of these diseases as distinct entities became possible with the recent recognition of the etiologic importance of hyperparathyroidism in generalized osteitis fibrosa cystica.[6] Furthermore, during the last few years, the pathologic basis for Paget's disease has been intensively scrutinized, especially by Schmorl,[7] with the view of establishing definite diagnostic criteria for the recognition of the disease both grossly and microscopically. It follows in the direct course of such investigations that efforts toward understanding the disease etiologically would be made, especially since it had been definitely set apart from other bone diseases.

TERMINOLOGY

The name "osteitis deformans" given by Paget because the bones of his patient showed gross thickening, elongation and deformity applies only to the advanced forms of the disease with involvement of many bones. Such a designation is not accurate in view of the fact that localized forms of involvement exist, frequently without apparent gross deformity. It appears that, for the present, it would be best to designate the condition as "Paget's disease" instead of "osteitis deformans." This permits the inclusion under one name of all degrees of bone involvement. It is only necessary to mention that since Paget's time a great number of other names, some quite descriptive, have been suggested for the condition.

OCCURRENCE

Man.—Paget's disease existed in ancient times, as study of the skulls and bones collected in various archeological museums shows. Butlin,[8] who carried out the microscopic studies for Paget, believed that the Neanderthal skull in the South Kensington Museum showed evidence of this disease, a view also held by Huxley, though others have claimed that the skull was rachitic. Stegmann [9] observed changes suggesting Paget's disease in the bones of the extremities and the vault of the skull in 5 of 1,000 skeletons of American Indians. As a clinical entity, however, it is a disease of modern times, and the case reported

6. (*a*) Mandl, F.: Arch. f. klin. Chir. **143**:1 and 245, 1926. (*b*) Collip, J. B.: Medicine **5**:1, 1926. (*c*) Barr, D. P.; Bulger, H. A., and Dixon, H.: J. A. M. A. **92**:951, 1929. (*d*) Jaffe, H. L., and Bodansky, A.: J. Exper. Med. **52**:669, 1930. Jaffe, H. L.; Bodansky, A., and Blair, J. E.: Arch. Path. **11**:207, 1931..

7. Schmorl, G.: (*a*) Verhandl. d. deutsch. path. Gesellsch. **21**:71, 1926; (*b*) **25**:205, 1930; (*c*) Fortschr. a. d. Geb. d. Röntgenstrahlen **43**:202, 1931; (*d*) Beitr. z. path. Anat. u. z. allg. Path. **87**:585, 1931; (*e*) Virchows Arch. f. path. Anat. **283**:694, 1932.

8. Butlin, H. T.: Lancet **1**:519, 1885.

9. Stegmann: Wien. klin. Wchnschr. **18**:619, 1905.

by Wilks is probably the first good clinical picture recorded in the English language.[2b]

There seems to be no particular geographic distribution of the cases, and there is no greater prevalence on the European than on the North American continent. The disease has been observed in the Japanese and in American Negroes. From the cases on record the disease seems to be somewhat more prevalent in the male, but during the last seven years more female than male patients with this disease have been seen in the Hospital for Joint Diseases. However, the sex factor is certainly of no etiologic consequence.

Animals.—The spontaneous appearance in animals of a condition simulating Paget's disease is of considerable interest, as it offers the possibility of an experimental approach to the study of the disease. The condition has been reported especially in monkeys kept in captivity In such animals, the bones of the extremities are thickened and deformed, and the skull bones may show involvement. White [10] detailed 3 instances of what she called Paget's disease appearing in monkeys which, after having been on a deficient, osteomalacia-producing regimen, had been changed to a high calcium diet for a period of 7 months preceding autopsy. Christeller [5] at about the same time described the pathologic changes in 5 monkeys, which in addition had considerable enlargement of the skull-bones.

More recently Hellner [11] examined the skeletons of 147 monkeys collected by Christeller over a number of years, and found that 21 per cent showed bone diseases. Fibrous lesions, the bones being either thicker or thinner than normal, constituted the preponderant condition. This study showed that the bones of animals originating on the American continent were either hypostotic or hyperostotic (thin or thick), while those of monkeys of other origins nearly always were hyperostotic, with enlargement of those of the skull. This may have some significance. It is the hyperostotic condition in these animals that shows a gross resemblance to fully developed human Paget's disease.

The enlargement of the facial bones in the monkeys induces an outward appearance resembling goundou. In Christeller's collection, the baboon most frequently showed hypertrophy and goundou-like involvement of the facial bones, but it should be indicated that this species shows a facial configuration that is normally in the direction of goundou, because of prominent cheek bones. Christeller denied that the facial changes observed in monkeys with diseases like Paget's disease were related to human goundou, and designated the condition as pseudogoundou. There is some similarity between pseudogoundou of

10. White, E. P. Corson: Arch. Int. Med. **30**:790, 1922.

11. Hellner, H.: Virchows Arch. f. path. Anat. **264**:238, 1927.

monkeys and the facial enlargement that occurs in the sniffling disease of swine, goats and horse.[42] That an infection may sometimes be the cause of the enlarged monkey jawbones is a possibility that cannot as yet be ruled out. It is the cause of the enlarged facial bones in the sniffling disease of swine, goats and horses. In the quadrumana, as in other animals, involvement of the facial bones is usually associated with disseminated bone involvement. Isolated hypertrophy of these bones occurs in man, but has not as yet been observed in monkeys.

Although there is this apparent gross similarity between the hypertrophic bone lesions of monkeys and human Paget's disease, their identity has by no means been established. Nor has there been experimental production of hypertrophic bone lesions in monkeys like those of Paget's disease. Because of this, and also because the histologic criteria of Paget's disease have been recently better defined, it was thought worth while to reconsider this apparent similarity.

Through the kindness of Dr. Fox and Dr. Radcliffe of the Laboratories of the Philadelphia Zoological Society, pieces of the rib, jaw and femur of the South American red woolly monkey, described by Corson White [10] as having Paget's disease, were obtained.

> The bones were thickened. The marrow cavity of the femur was nearly completely obliterated. Histologically there was complete disappearance of the original bony tissue. In its stead, there was a moderately cellular connective tissue in which considerable new fiber bone formation was in progress. Some of this bone was being ossified, although much of it was still uncalcified. There was little, if any, transformation into lamellar bone, and no cement lines were present. Few osteoclasts were seen. The narrowed marrow cavity of the femur contained myeloid cells, and there was no connective tissue scarring. Both the periosteum and the endosteum participated in increasing the thickness of the femur. The marrow cavity of the rib was completely obliterated. Many tiny cystic spaces were observed in the loose connective tissue of the bones examined.

The lesion described is a very extensive fibrous osteodystrophy with concomitant thickening of the bones, and aside from the suggestive appearance created by the thickness of the bones, the lesion neither grossly nor microscopically resembles advanced human Paget's disease, as encountered by the pathologic anatomist. There can be no doubt that many others who described spontaneous Paget's disease in monkeys were detailing this hypertrophic fibrous osteodystrophy to which monkeys seem subject. Christeller himself was misled, primarily because he recognized Paget's disease merely as a hypertrophic fibrous osteodystrophy.

The hypertrophic fibrous osteodystrophy appearing in Corson White's monkeys was associated with a dietary imbalance. Her first animals, after having been on a deficient, osteomalacia-producing diet,

12. Christeller.[5] Jaffe and Bodansky.[6d]

presented thickened bones within 7 months after being placed on a corrected diet rich in calcium. Subsequently she found that monkeys on a diet poor in calcium, phosphorus and protein, as measured by man's requirements, frequently showed severe osteomalacia, but less often hypertrophic osteitis, which was called Paget's disease.[13] Sunlight was only slightly preventive. The age of the animals is not given. Hypertrophic bone lesions are not encountered as frequently as porotic in experimental animals. Nevertheless, thickening of the bones developing as a result of an obvious disturbance of the dietary regimen should not necessarily be designated as Paget's disease. In man, Paget's disease is certainly not associated with an unbalanced diet such as that mentioned.

Another type of lesion is encountered even more frequently in monkeys. Dr. Alfred Plaut, director of Laboratories of the Beth Israel Hospital, New York City, sent me the bones of 2 capuchin monkeys (which died in captivity) illustrating this type of reaction. One was about 3 years of age and the other somewhat older. The bones were not thickened, except those of the forearm. These were deformed, and showed moderate subperiosteal new bone formation, particularly on the convex surface. All of the bones were apparently soft. They showed enlargement of the canals in which the blood vessels run and, in the younger monkey, a considerable increase in the connective tissue in these canals. The number of osteoclasts was negligible. The striking histologic feature was the subepiphyseal and costochondral osteosclerosis. Rather thick and compact trabeculae of lamellar bone were observed in these regions. The changes in many ways resembled those due to phosphorus, arsenic and lead poisoning in growing animals rather than those of Paget's disease, though they could be mistaken for and included with the fibrous bone lesions.

Nevertheless, the conception that the hypertrophic bone disease of monkeys and human Paget's disease are similar is still accepted without much critical analysis. Rohr,[14] examining 2 monkeys with hypertrophic bones, reported that on histologic examination these bones showed numerous irregular cement lines, the presence of which has been considered important in making a microscopic diagnosis of Paget's disease (see under "Microscopic Anatomy"). He assumed from this that additional evidence existed for considering the hypertrophic bone lesions in the monkey as analogous with those of human Paget's disease. However, the only photomicrograph to show numerous and irregularly disposed cement lines that Rohr publishes is from the jaw of one of his animals. This picture is not convincing. Furthermore, it is hazard-

13. White, E. P. C.: Rep. Zool. Soc. Philadelphia, 1931, pp. 11 and 31.

14. Rohr, P.: Inaugural Dissertation, Pathological Institute, Basel, Berlin, Julius Springer, 1931.

ous to accept a basic relationship between the bone changes of human Paget's disease and those observed in his monkeys solely on the *local* existence of this histologic criterion. Such cement lines may only be evidences of a healing process. I have observed an abnormal number of irregular cement lines in chicken bones in which hypertrophy had been experimentally produced, although the lesion was certainly not Paget's disease. I have also seen numerous cement lines in the femur of a dog which, after removal of three parathyroids, was on a meat diet without supplementary calcium for about 10 weeks. This animal had several attacks of tetany. A healing infectious periostitis with excessive bone formation may easily produce the histologic changes described in the jawbones by Rohr. Furthermore, since the jawbones are subject to functional trauma incident to mastication, they normally show many more cement lines than other bones. These are often irregularly disposed, and they are an expression of active transformation constantly taking place in these bones.

In conclusion it may be said that while the hypertrophic lesions in some monkey skulls may suggest leontiasis ossea, and while the disseminated hypertrophic bone lesions in other animals may suggest Paget's disease, the identity of the lesions with human Paget's disease is far from proved.

RELATION TO AGE

Paget's disease is observed clinically chiefly in persons past the age of 40. This seems to be of etiologic importance; age is to be considered whenever a question of diagnosis is raised. The records of this hospital are in line with this view: Most of the patients were 50 years old or older when the disease was first observed. The disease is most frequent between the ages of 60 and 70. It may, however, be 10 or 20 years or longer before the condition becomes fully developed clinically. I recently saw a man 48 years of age suffering from Paget's disease, in whom the first symptoms appeared 20 years ago. Schmorl [7e] stated that he had never observed the pathologic changes of Paget's disease, no matter what the degree, in persons under 40 years of age. It is difficult to accept such an abrupt age relationship. One or two fully developed cases have been recorded as occurring in persons below the age of 20, but such cases should always be looked on with suspicion and accepted with caution. Now and then one hears of a case of adolescent Paget's disease, the bones being thickened and deformed and the tibiae curved. These changes must not be confused with renal rickets. As yet nothing definite is known about such cases.

FAMILIAL FACTOR

Several cases of Paget's disease have occurred in the same family. The significance of this is unknown.

FREQUENCY

The *classic disseminated, or polyostotic,* form of Paget's disease (as described by Paget) is not very usual. In 1901, Packard, Steele and Kirkbride [15] collected 66 published cases. According to Hurwitz,[16] 175 cases were recorded by 1913. It is safe to estimate that only about 500 cases of disseminated, or polyostotic, Paget's disease have been reported by now. The relative rarity of advanced Paget's disease as observed in the clinical services of large hospitals may also be gaged in another way. Of Hurwitz' 6 reported cases, 3 were from the records of over 30,000 medical admissions to the Johns Hopkins Hospital, and 3 were from a larger number of admissions to the Johns Hopkins Dispensary. Cutler [17] gathered 7 cases from 285,000 outpatients observed at the Massachusetts General Hospital during a period of 12 years. Carman and Garrick [18] recorded 15 cases from among 237,000 admissions to the Mayo Clinic.

The number of clinical cases observed by any individual often varies with his interest in the disease. Locke [19] had personally studied 40 polyostotic cases in 12 years. Within 4 years, without a definite search, I have had about 20 cases brought to my attention from among the patients of this hospital and dispensary, although the records of the hospital show a number of additional cases.

When the incidence of the disease is approached from the point of view of the pathologist, some new and interesting facts come to light. A number of continental pathologists interested in bone diseases have observed Paget's disease often enough to accumulate considerable experience. Pick,[20] during the past 25 years, has encountered 30 cases in which he confirmed the gross diagnosis by microscopic examination. His material comes chiefly from cases with polyostotic disease, but includes a number of specimens from cases with involvement apparently of a single bone.

Schmorl's findings impress one with the necessity for a revised point of view. Prior to 1925 he observed 25 instances of what he classed as "osteitis fibrosa" in 32,000 autopsies (this included Paget's and the rarer von Recklinghausen's disease). While pursuing his epoch-making studies on the pathology of the spine, he turned his attention to "osteitis fibrosa" and within 6 months added 18 additional instances by examining

15. Packard, F. A.; Steele, D. J., and Kirkbride, T. S.: Am. J. M. Sc. **122:** 552, 1901.

16. Hurwitz, S. H.: Bull. Johns Hopkins Hosp. **24:**263, 1913.

17. Cutler, E. C.: Boston M. & S. J. **174:**187, 1916.

18. Carman, R. D., and Garrick, W. M.: J. Radiol. **2:**7, 1921.

19. Locke, E. A.: Personal communication to Hurwitz.[16]

20. Pick, L.: Verhandl. d. Gesellsch. f. Verdauungs- u. Stoffwechselkr., X-Tag., 1931, p. 146.

systematically 650 skeletons (skull, spine and a lower extremity).[7a] Nearly all these were what he recognized as Paget's disease. By 1930 he had collected 114 examples of what he termed Paget's disease;[7b-c-e] by 1931, about 150, and by 1932, 190. Paget's disease was observed by him 138 times in his last 4,614 autopsies on persons past 40 years. This makes an incidence of about 3 per cent in persons past 40 when the frequency is arrived at by systematic pathologic examination of the skeleton.[7e]

One is taken by surprise by such postmortem statistics, and they require clarification. One had previously understood that the disease is comparatively rare. It should be taken into account that the increased incidence of Paget's disease which Schmorl's reports show is not due to an increase in the number of persons showing the classic deforming osteitis that Paget described—they are still rather uncommon clinically. The increase in the incidence of Paget's disease arrived at by Schmorl is due to the inclusion in these statistics of numerous examples of subclinical or nonclinical stages of the disease. He has pointed out that Paget's disease is frequently to be found in the lumbar vertebrae, the sacrum or the bones of the pelvis, separately or in combination, frequently in the absence of gross anatomic implication of any other bones. He has even included 4 cases in which the diagnosis was only finally made microscopically.

GROSS ANATOMY

The more recent work on the pathologic anatomy of Paget's disease indicates that much of the older conception of its pathologic picture must be modified and amended. Whatever developments may come from this newer work, there is no doubt that the advanced form of the disease with its disseminated, or polyostotic, changes remains as a clearly distinct clinical type—in all respects the same as when Paget described it. In many of these cases there is apparent simultaneous involvement of many bones, with rapid progress and resultant deformity. However, the newer work has demonstrated that bone changes in every way characteristic of those observed in the disseminated form may be encountered (especially in the pelvic, sacral and vertebral bones) in the absence of clinical signs or symptoms. Whether, in the polyostotic cases, the disease had first remained localized in the pelvic bones, sacrum or spine, and then rapidly progressed in these and other bones, cannot be determined at this time.

Schmorl was able to show on systematic examination of a great number of skeletons that Paget's disease is most often found in the spine, including the sacrum; in fact, it is often present exclusively in the spine. He found the lesions in Paget's disease in the sacrum or vertebral bones in each of 138 cases systematically studied. Usually

only a single or a few vertebrae or vertebral groups showed pathologic changes, while complete involvement of the spine occurred only 4 times.[7e] The gross and microscopic appearances of the diseased areas in such cases are in every way like those found in the cases with advanced lesions, only the involvement is not so extensive. When only a part of the sacrum or of the pelvis or a single or a few vertebrae are diseased, it is readily comprehended why clinical evidences of the disease may be absent. In such nonclinical cases there may be at most a history of pain. As indicated, it is this type of Paget's disease that has increased the anatomic incidence to about 3 per cent in all patients past 40 years.

Furthermore, Schmorl had been paying special attention to even earlier stages of the disease in which small foci consisting of thickened trabeculae are present, especially in the lumbar vertebrae or in the sacrum; the intertrabecular marrow is frequently not even scarred. Such foci of thickened trabeculae may be so small as to require the use of a hand magnifying glass for their satisfactory identification at the autopsy table. A final diagnosis of Paget's disease was made in these cases only on histologic examination.

In addition, it seems definitely established that Paget's disease must be viewed as a local disease, even though it may affect practically the entire skeleton. If only a single bone or skeletal part is involved, the disease is termed monostotic. In considering the monostotic form of Paget's disease, one must differentiate between clinical and pathologic concepts. While it is true that from the pathologic point of view there is a great tendency for the disease to remain localized to a skeletal part or system, the greatest number of such cases are not clinical problems, because the bones usually so involved are those of the pelvis, sacrum and spine, and no clinical symptoms or signs direct attention to the disease. When, however, the lesion is localized to a long tubular bone, a clinical picture may be created that invites attention.

Schmorl analyzed the frequency of involvement of single skeletal parts in 138 cases, and pointed out that in view of his findings it is incorrect to state, as practically all previous publications do, that the skull, tibiae and femora are the bones most often involved.[7e] His anatomic studies indicate that the spine, including the sacrum, is most subject to the disease, which, when it attacks the spine, usually involves only a single vertebra or several.

The sites of earliest localization have been coordinated with the sites most subject to the mechanical effects of function. The validity of this conception seems supported by the anatomic findings, which indicate that the sacrum, which carries the entire weight of the torso, is the bone most frequently diseased, while the lumbar vertebrae are twice as often involved as the thoracic and thrice as frequently as the cervical. The

frequent implication of the femora and pelvic bones as against the rare involvement of the scapula seems to speak for this view, as does the common involvement of the sternum and clavicles. However, the relative immunity of the jawbones, which are constantly subjected to the mechanical trauma of mastication, and the frequency of skull involvement will have to be explained before functional trauma can be given an all-important position in regard to localization. Those who consider functional trauma as important for localization hold that the calvarium thickens often, possibly, because there are continued pulsation of the brain and a marked pull of the neck muscles, added to which is the trauma of mastication.

A case of Paget's disease recently came under my observation; the bones obtained at autopsy permit the study and the demonstration of some of the newer aspects of the pathologic anatomy of the disease.

Frequency of Paget's Disease in Single Skeletal Parts (Schmorl's 138 Cases)

Bone	Frequency	Per Cent
Sacrum	78	56
Spine (lumbar vertebrae most often)	69	50
Right femur	43	31
Cranium	39	28
Sternum	32	23
Pelvis	30	21
Left femur	21	15
Clavicle	18	13
Tibia	11	8
Ribs	10	7
Humerus	6	4

A woman, 64 years of age, entered the hospital with a complete transverse fracture at the junction of the proximal and middle thirds of the shaft of the left femur. This fracture had resulted from an accidental fall four months prior to admission. The patient had had pain in both thighs over a period of many years, becoming more severe during the last four or five years. There was limitation of flexion of the right thigh. It is interesting, if not significant, that during the last few years, in going upstairs, she found it necessary to favor the right extremity, putting all her great weight (for she was an obese woman) on her left lower extremity. For a number of years she had had pain in her back, particularly on bending. In 1924, she had been admitted to another hospital, where a diagnosis of Paget's disease had been made on the basis of roentgenologic examinations of her lower extremities. Roentgenologic examinations at the Hospital for Joint Diseases showed that the skull was apparently uninvolved; the left ilium and the sacrum, on the contrary, showed distinct changes; the left femur disclosed a recent complete transverse fracture at the junction of the proximal and middle thirds of the shaft, with pronounced internal displacement of the upper end of the distal fragment and distinct cortical and periosteal thickening; in the right femur, the changes of Paget's disease were discernible roentgenologically only in the upper end; there was punctate osteoporosis of the lower ends of the right tibia and fibula, while the left tibia and fibula appeared normal. Within a few hours, following an attempt at open reduction of the ununited fracture of the left femur, the patient died.

The gross anatomic characteristic as regards the bone in this disease is the removal of the normal osseous structure and its replacement usually by excessive amounts of new bone formed on a more porous plan.[21] The excessive bone formation may possibly be in compensation for the new bone, which is of poorer quality than the normal bone. Whether part of a bone, an entire bone or many bones are diseased, the pathologic changes may be considered as a whole—variations due to degree of involvement being considered as the individual bones are discussed.

In the advanced stages, the recognition of Paget's disease at the autopsy table is relatively simple. Even milder degrees of involvement may be recognized with fair ease, especially by those experienced with the disease. This is particularly so when the early stages are found to involve spongy bone, the trabeculae of which are normally of more or less uniform thickness (vertebrae, sacrum, sternum, pelvic bones).

Figure 1 shows the lower portion of the spine in the case just described. The bodies of the eleventh and twelfth dorsal and the upper four lumbar vertebrae are slightly osteoporotic, the fourth lumbar vertebra showing a reduction in the superior-inferior diameter. The fifth lumbar vertebra appears completely different: thick, irregular and interlacing trabeculae replace the normal ones. This is the case immediately beneath the intervertebral disk cartilage plate, where the trabeculae become so densely set posteriorly near the posterior ligaments as to simulate cortical bone. The various processes of the body also show this complete transformation. This is in harmony with what will be pointed out later —that when Paget's disease involves a vertebra, the entire bone soon becomes more or less uniformly diseased. Figure 1 *B* presents the macerated specimen obtained from the fifth lumbar vertebra, in about natural size. One may easily discern the thick, somewhat irregularly set, dull-white trabeculae, in honeycomb-like arrangement, with tooth-like trabecular surfaces; also the condensation of the bone posteriorly, creating a compact structure. The intertrabecular spaces contained cellular tissue before maceration.

It is more difficult to diagnose the earlier stages of the disease in the long tubular bones. This is due to the fact that normally at the spongy ends of such bones there are trabeculae of variable thicknesses. Thus, when the degree of involvement of the trabecular ends of the tubular bones is such that a diagnosis of Paget's disease is evident, the rest of the bone—that is the compacta—is already grossly diseased. As regards the compacta, the earliest stages of the disease cannot be recognized grossly, and they were found microscopically only twice by Schmorl. In the long tubular bones the disease begins in the spongiosa of the upper

21. Knaggs, R. L.: Brit. J. Surg. **13**:206, 1925-1926.

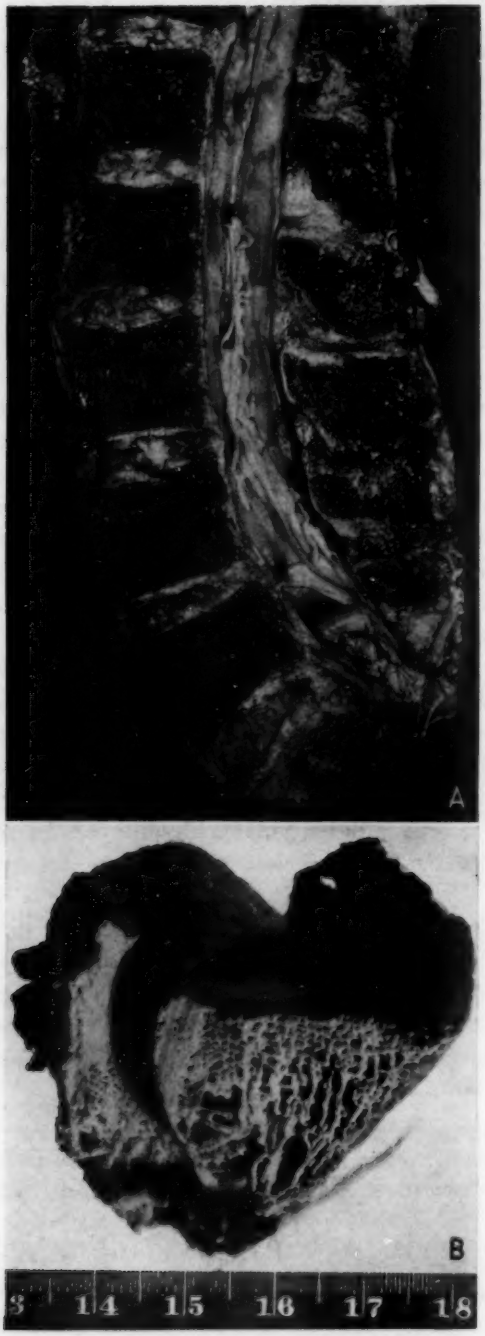

Fig. 1.—*A*, wet specimen of the lower portion of a spine with Paget's disease limited to the fifth lumbar vertebra; *B*, the fifth lumbar vertebra after maceration. Thick, somewhat irregularly set, dull-white trabeculae with a honeycomb-like arrangement are seen in *B*; these are so densely set posteriorly as to simulate cortical bone. The enlargement is about 20 per cent.

and lower ends and progresses toward the middle of the diaphysis with a slowly increasing thickness of the compacta, which finally may take on a lamellated appearance.

When the disease is fully developed, both the external and the internal appearances of the long tubular bone are modified. When a thickened and deformed long tubular bone in an active case is opened, it is observed that the cortex is vascular and has a spotted grayish-red color. In the progressive stages of the disease, an extensively involved bone may be so soft that it can be cut with a knife, or certain portions of it will cut easily while here and there somewhat sclerotic and nonyielding areas are encountered. Such bones usually show enlargement of the circumference and of the sectional area. In the case described, the surface of the left femur, when the muscles were removed, presented an irregularly knobbed appearance. The periosteum was intact throughout

Fig. 2.—The subperiosteal pumice-like outer surface of the lower portion of a macerated femur.

and showed injection in many places. On stripping off the periosteum, which was fairly adherent to the underlying spongy cortex, an irregular, roughened bony surface was exposed that showed injection and suggested subperiosteal osteophytic new bone; in many ways, the exposed cortical surface was reminiscent of the bone observed underneath the periosteum in the presence of inflammatory osteoperiostitis. Figure 2 shows the pumice-like subperiosteal surface of the lower portion of the macerated femur. The knobby irregularity of the surface is also clearly indicated.

The cortex was of variable thickness and was thickest in the vicinity of the fracture, where it measured 2 cm.; it measured 13 mm. at 12 cm. from the lower end of the femur. At this point, the cortex showed a distinct division into two layers—an outer zone of about 4 mm., consisting of injected, spongelike, periosteally formed bone, and an inner zone of more compact, somewhat lamellated, whitish, dense and sclerosed

bone. On the inner, or endosteal, surface, this more or less compact, lamellated, cortical bone showed marked resorption and erosion (fig. 3). Within the cortex proper, many large spaces with irregular walls were observed, which were filled with fat. These were particularly prominent in the deeper layers of the lamellated, compact bone. Figure 3 shows these cystic spaces within the cortex and also a distinct demarcation between the outer subperiosteally formed cortical bone and the

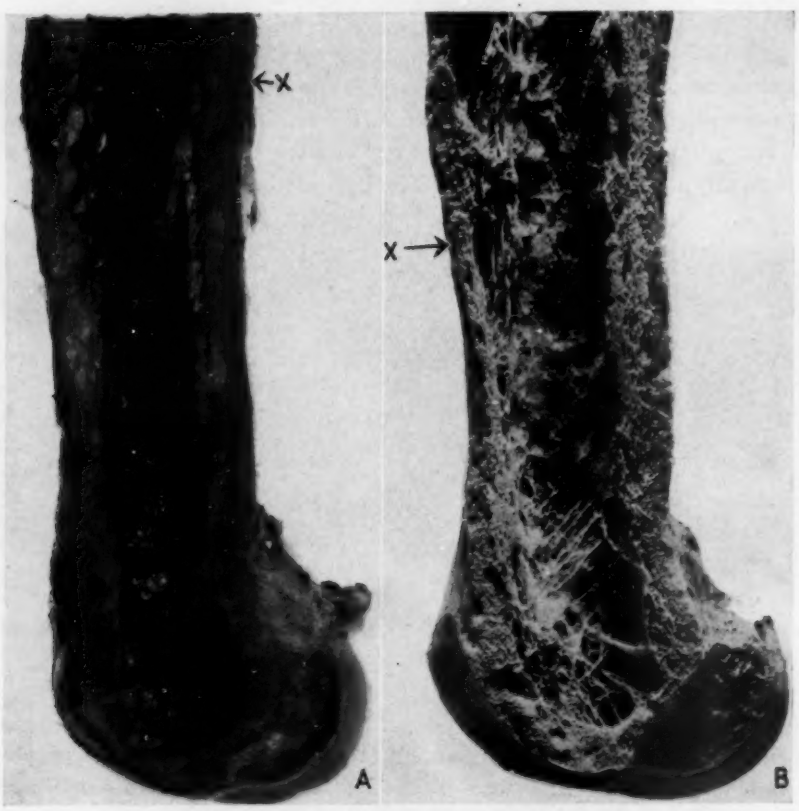

Fig. 3.—*A*, fresh specimen of the lower end of the femur; *B*, the same specimen after maceration. In *A*, the variable thickness of the cortex is to be observed. The cortex shows distinct division into two layers—an outer zone of periosteally formed bone, and an inner zone of more compact, somewhat lamellated Paget's bone. In *B*, cystic spaces within the cortex and the great irregularity of the endosteal surface with thick trabeculae at the distal end are to be observed. The sharp demarcation of outer spongy and inner more compact, lamellated bone is plain.

deeper lamellated cortical bone. It also shows the great irregularity of the endosteal surface of the lower end of the femur and the thick, irregular trabeculae at the distal end.

The entire femur, as has been indicated, was involved. In the upper third, the picture was much more confused. As will be observed in figure 4, the cortex of the inner surface of the femur in the vicinity of the neck was dense and sclerotic, and grossly lamellation was only suggested. The neck was shortened and rotated so that the head was almost at right angles to the shaft, producing coxa vara. The greater

Fig. 4.—A fresh specimen of the upper portion of the femur. The neck is shortened and rotated. The greater trochanter juts out above the head. Fat-filled cystic spaces are observed in the femoral head and neck.

trochanter jutted out above the head. It showed marked thickening of the borders, which were lamellated, and it contained spaces filled with fatty marrow. Such fat-filled spaces were also observed in the femoral head and neck, and created, roentgenologically, cystlike appearances. This was also the case, as was pointed out, in the shaft. Figure 5, which is a roentgenograph of a freshly removed specimen, demonstrates these

cystlike spaces, which Freund [22] has discussed in an important paper, and designated as pseudocysts.

In describing the cortex of the femur in this case, it was shown that the cortical layer was composed of two zones, an outer rather spongy and pumice-like zone and an inner rather compact, dense, white and lamel-

Fig. 5.—A roentgenograph of the specimen shown in figure 4. The cystlike spaces are more clearly observed, and the outer periosteally formed cortex, particularly on the right side, stands out prominently.

lated zone. This division was plainly observed both in the wet and in the macerated specimens with the naked eye and roentgenographically (figs. 3 and 5). It must be pointed out that such a gross division of the cortex is exceptional, and the observation of such specimens has led

22. Freund, E.: Virchows Arch. f. path. Anat. **274**:1, 1929.

to establishing beyond doubt that periosteal activity is the basis of the thickening of cortical bone in this disease. While it has been believed by some that the periosteum participates in the growth in thickness of tubular bones (see Paget's first paper), it remained for Freund [22] to demonstrate conclusively the part played by the periosteum in this cortical thickening. Since then his work in this regard has been fully confirmed by Schmorl.[7e]

It is curious that patients in whose bones periosteal participation was manifested in the gross had fractures and were bedridden for various periods of time. The case that I have described, in many respects, was an exact counterpart of Freund's; his patient suffered a fracture of the neck of the femur and was bedridden for about 8 years. As in my case, the gross periosteal bone formation was observed in the fractured femur. In all of Schmorl's [7e] extensive material only two examples of gross periosteal bone formation are described, and curiously enough both examples are from patients who had sustained fractures and been bedridden for a period of time. In 1 of his cases, with a fracture of a femur, the periosteal proliferation was observed grossly in the opposite femur. He is at a loss to account for the mechanism underlying the change in this case and offers an explanation somewhat as follows: A fracture through the diaphysis of the left femur had occurred 15 months before death and the patient was confined to bed for 4 months after the fracture; during this time of inactivity, atrophy had set in, embracing the femora involved in Paget's disease; when the patient was permitted to leave his bed, he favored his left femur, and the functional irritation to which the atrophic right extremity was subjected necessitated rapid periosteal bone proliferation to produce additional, though statistically inferior, bone for support. In Schmorl's second case in which periosteal proliferation was observed grossly, the proliferation was in a bone that had sustained a fracture some time previously.

In my own case, gross evidences of periosteal activity were observed throughout the shaft of the femur on the side of the fracture. The periosteal new bone was, in places, from 4 to 5 mm. thick. On the basis of the histologic examination I must reach the conclusion that the periosteal new bone formation in this case was distinctly purposeful, for microscopically there was considerable evidence of aseptic necrosis of the inner, older and more compact bony zone, particularly in the vicinity of and at some distance above and below the site of fracture. As will be shown when the microscopic anatomy of Paget's disease is discussed, histologic evidence of periosteal proliferation is not in the least unusual. The appearance of gross periosteal bone formation is the result only of an exaggeration of a process normally present in many cases of

Paget's disease; the excessive periosteal proliferation being merely an exaggeration of the process induced by the complication of the fracture.

Earlier recognition of periosteal activity in Paget's disease is obscured by the fact that the periosteal bone formation is generally at any given time so slight as to require careful microscopic study of the specimen. Furthermore, the periosteally proliferated bone rapidly becomes diseased and fuses with the rest of the transformed cortex so that the distinction between them is obliterated and the former therefore escapes identification. In contradistinction, it is much simpler to demonstrate periosteal thickening in association with inflammation or with syphilis, because with these conditions the underlying cortex is frequently little involved. In fact, until recently the nonparticipation of the periosteum was considered typical of Paget's disease by most pathologists. Weber, reflecting the opinion of Aschoff and of Pick (who have by now probably become convinced of periosteal activity in this disease) as recently as 1927 denied the participation of the periosteum in the production of the pathologic lesion, and stated that the lesion began in the medullary cavity.[23]

Schmorl stated that periosteal thickening begins with complete transformation of the cortex, while resorption at the medullary surface is taking place. Freund believes that the parosteal tissue participates in the periosteal new bone formation, and this seems to be correct for his case. My own case also suggests the possibility of parosteal bone formation. Thus, it is now established that the thickening of a tubular bone in Paget's disease is entirely a matter of periosteal thickening.

The appearance of the medullary cavity of a completely diseased tubular bone varies considerably. When the bone is diffusely involved, it is nearly always widened. Knaggs, who studied the collected material in the Museum of the Royal College of Surgeons, stated that in some macerated specimens the widened interior of the bone shows a very open arrangement of trabeculae with irregular spaces between them; in other specimens, the central cavity is much elongated and often irregularly enlarged, its boundaries being unevenly sclerosed, and containing at the same time many open longitudinal spaces; in still other specimens, a contracted but elongated central cavity is seen.[21] An enlarged marrow cavity may rarely extend to the articular ends of a bone, and the bony end-plate is apt to be of paper-like thinness, and may in part be absent. Fat-filled marrow spaces, delineated by thickened sclerotic trabeculae of bone may produce in x-ray pictures the appearances of cysts, as stated. Figure 3 *B*, picturing a macerated preparation from the lower half of the femur, shows the bizarre appearance that the medullary cavity may assume. Variations in the appearance of the

23. Weber, M.: Beitr. z. path. Anat. u. z. allg. Path. **78**:441, 1927.

medullary cavity are dependent on the stage to which the disease has progressed as well as on other associated factors (deformity of the bone, etc.).

The so-called endosteal form of Paget's disease, which has been described by Pick and others, and which was reviewed by Stenholm,[24] shows obliteration of the marrow cavity by fine spongy bone substance. This condition is rare, and there is a strong possibility that it is not Paget's disease. It has been described mostly in young subjects.

In regard to other tubular bones: The tibia, when it is diseased, shows diffuse involvement and becomes curved and thickened; its marrow cavity is usually enlarged and the cortex lamellated.. However, the tibia may escape even when many other bones are diseased. In Freund's case, the tibia (on the side of the fracture) was markedly atrophic, this apparently being attributable to inactivity. In my case, with extensive disease of the right femur, the right tibia was atrophic but offered no evidence of Paget's disease. Curiously, the fibula seems to show practically no disposition to the disease. One of the striking and rather frequent roentgenographic features of the leg in advanced cases of Paget's disease is thickening and bending of the tibia, while the fibula remains straight and radiologically normal. On the whole, the short tubular bones seem to be exempt from the disease, but no pathologic investigations have been carried out to give absolute confirmation of this. The difficulty of obtaining such specimens is obvious.

The articular cartilages seldom show any significant deviation from the normal. Inflammatory changes are rather uncommon in spite of the frequently advanced age of the patients. The articular cartilages may show passive implication, attributable to attrition, the result of malalinements of the joints. In my case, the articular cartilage of the condyles of the fractured femur was definitely atrophic and rigid; the process was more marked anteriorly, but there were no osteophytes. The articular cartilage of the head was also atrophic and in places definitely ulcerated, so that sclerotic underlying bone was exposed; osteophytes were also absent in this region. However, Freund reported that in his case there were severe changes in the articular cartilages overlying diseased areas, and that these changes, on microscopic examination, were not entirely typical of arthritis deformans. The joint exostoses that were observed in his case showed the microscopic structure that is more or less typical of Paget's disease.

The cranium is usually exceedingly altered in structure in the polyostotic cases. The changes manifest themselves principally in the calvarium, which, when it is diseased, is frequently diffusely involved; the degree of thickening, however, may be irregular. As a rule, the

24. Stenholm, T.: Osteodystrophia fibrosa, Uppsala, Almqvist & Wiksell, 1924.

thickening of the calvarium is most marked in the occipital regions. The circumference of the skull may increase considerably; in Paget's case it enlarged from 53.3 to 67 cm. The increase in size of the calvarium takes place almost entirely outward, and the thickening is the result of the deposition of parallel fine-fibered bone on the outer table; the new bone is slowly transformed into Paget's bone. The suture lines are obliterated.

Changes in the calvarium are frequently associated with great vascularity, which is sometimes severe enough to suggest venous thrombosis. In the vascular stage, the bone is of a marked speckled red color due to permeation from side to side by a vascular connective tissue marrow. Schmorl observed 5 cases in which the hemorrhagic discoloration was so severe as to suggest hemorrhagic infarction.[7e] Circumscribed osteoporosis of the cranial bones has been described as an early stage in their involvement.[25] This roentgenologic picture may be caused by areas of local resorption associated with increased vascularity.

Knaggs stated that the cranial bones finally go through a stage of advancing sclerosis during which the vascularity wanes and the outer and inner surfaces become bounded by condensed bone of varying thickness. The intervening portion shows various degrees of porous, cavernous or cancellous tissue the spaces of which are filled with soft reddish substance. Following this there may be, according to Knaggs, a stage of diffuse sclerosis, in which the sclerotic tissue advances across the diploic zone, sometimes extensively. He found in sclerotic calvaria islets of ivory bone surrounded by lines of demarcation, which suggested that they might eventually become sequestrums.[21]

The base of the cranial cavity may appear normal in some advanced cases with disease of the calvarium, but in a fair proportion it is obviously involved. The grooves for the meningeal vessels are deep and sharply marginal, and the pituitary fossa may be altered. The various neural foramina are not seriously contracted, though the regularity of their margins may be disturbed. This is noticeable in the foramen magnum. On the other hand, the vascular foramina have occasionally been reported enlarged, presumably the result of pressure exerted on the softened margins by the pulsation of the transmitted vessels.

As the facial bones are rarely correspondingly altered, the face appears much smaller. But if the facial bones do become severely involved, the appearance may resemble leontiasis ossea. In such cases, in contradistinction to leontiasis ossea, the bones of the lower jaw are the ones usually involved rather than those of the upper. The frontal

25. Schueller: Med. Klin. **25**:631, 1929.

sinuses are usually found open, but they tend to become smaller and even entirely closed off in advanced cases, but this tendency is not as marked as in leontiasis ossea. Leontiasis ossea, in which there is hyperostosis localized to facial bones, has been regarded by some authors as a form of Paget's disease in which the morbid processes are confined to the bones of the skull.[26] However, the skull bones in cases of leontiasis ossea are exceedingly heavy compared with the hypertrophied skull bones of Paget's disease.

The reason for the frequent escape of the facial bones, so far as marked gross involvement is concerned, is not known. It remains one of the problems that must be elucidated. These bones are infrequently examined compared with those of the extremities. Possibly slight pathologic changes would come to light on their microscopic examination, with a demonstration of minor variations from the normal.

The attention with Schmorl directed to the spine in his already classic studies on the intervertebral disks was largely responsible for considerable revision of the conception of the pathologic anatomy of Paget's disease. As has been pointed out, it seems established beyond doubt that the spine, including the sacrum, is the skeletal part most often involved in Paget's disease. The disease is most frequently localized to the lower lumbar region and the sacrum, and when long tubular bones or the skull are free from pathologic changes those sites constitute the most common regions for nonclinical Paget's disease. Most often a single or a few vertebrae show pathologic changes. When only a few vertebrae are diseased, the entire vertebra is usually involved, but rarely is the disease limited only to the body.

The pathologic picture may be variable; the entire spongiosa of an involved vertebra may appear thickened while individual trabeculae are dull white and lusterless. The peripherally situated trabeculae may be closely set so as to frame the vertebral body, while the more centrally placed trabeculae are less densely placed, though the individual trabeculae are quite plump and thickened. They are likely to stand out as pillars with irregular surfaces. Under these circumstances, the marrow spaces in the spongiosa are irregular in size, and are frequently large, the latter sometimes being filled with a fine mesh-work of bone visible in the gross. These changes are clearly demonstrated in figures 1 *B* and 6 *A*.

As Schmorl [7e] pointed out, deformation of the diseased vertebrae is not unusual; there may be reduction of the superior-inferior width and the body appears sunken, which occurs when the intervertebral disks retain their expansive resilience; the dorsal-ventral diameter may sometimes be increased owing to slight periosteal proliferation; more

26. Hamburger, L. P., and Nachlas, I. W.: Arch. Surg. **12**:727, 1926.

rarely the size of the body is increased in all dimensions. If a few successive vertebrae are involved, the disease process may extend through the intervertebral disks when these are penetrated by blood vessels and connective tissue, the bone replacing the disk becoming changed to Paget's bone, and the several adjacent vertebrae becoming fused. When the entire spine is involved—and this rarely occurs unless there is very extensive disease in many other bones—marked spinal curvature may occur. On the other hand, as Schmorl has indicated, the kyphosis may be due only to extensive senile osteoporosis. With marked deformity, lipping of the bodies with synostosis of the margins at their articular surfaces and ankylosis may occur; the bone bridging the vertebrae may be transformed into Paget's bone. In the advanced cases, the spinal canal may sometimes be diminished in caliber owing to enlargement of the bodies and the bone composing the vertebral arches. This may be pronounced enough, as indicated by Knaggs, to reduce materially the perithecal space about the cord and its membranes. This is in line with the reduction in size of the posterior cranial cavity. In such cases, additional localized pressure points may result from the formation of osseous excrescences springing from the posterior surface of the bodies and other parts of the wall of the canal.

With regard to the rest of the thoracic bones: The entire sternum may be involved, or often only the manubrium, or body. Involvement of the rib occurs only in the polyostotic cases, and the process may be most severe in the axillary regions. Schmorl described changes of Paget's disease in the ossified portions of the costal cartilages, which may lead to considerable enlargement of these cartilages in the vicinity of the costochondral junction. (The appearance normally of bone in these sites in old persons is well known. Erdheim [27] described the occurrence of considerable pathologic changes in the costal cartilages in an old woman with pituitary derangement of the nature of acromegaly, at an age at which gross disturbances of the long tubular bones cannot occur.) Sometimes the clavicles are diffusely diseased, and at other times the lesions are only at the ends. The scapula when diseased, is likely to be only partly involved.

In regard to the pelvic girdle, the frequent involvement of the sacrum has already been stressed; most often it is only partly diseased. Diffuse involvement of the innominate bones is most frequently observed in the polyostotic cases when, because of the deformity, the pelvic outlet may become narrowed, as in osteomalacia. More often, however, only one or the other of the innominate bones is diseased, and then

27. Erdheim, J.: Die Lebensvorgaenge im normalen Knorpel und seine Wucherung bei Akromegalie, Berlin, Julius Springer, 1931.

only partly. As may be observed in figure 6*B*, there is diffuse disease of the superior ramus of the left pubic bone while the superior ramus of the right pubic bone is free; the disease thus stops abruptly at the symphysis.

The occurrence in Paget's disease of cysts and giant cell tumors as seen in von Recklinghausen's disease is definitely eliminated; in those reports in which such descriptions appear, careful scrutiny reveals

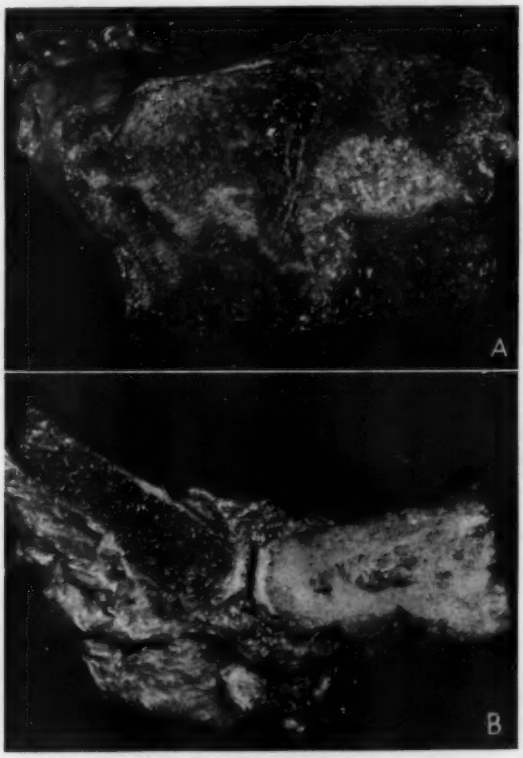

Fig. 6.—*A*, the sacrum, the sacro-iliac joint and portions of the ilium; very extensive Paget's disease of the sacrum is present with slight involvement of the ilium. *B*, the symphysis pubis and the superior ramii of both pubic bones; the right is completely free from Paget's disease while the left is diffusely involved and enlarged.

that the author was not dealing with Paget's disease. Cystic spaces and cavities are, however, frequently seen in Paget's disease. They result especially from liquefaction of the connective tissue and bone in small areas in which hemorrhagic or anemic necrosis has occurred.

Considerable changes take place in the physical character of bones involved in Paget's disease. The lightness of a macerated bone indi-

cates reduced mineral content, and in spite of the increased thickness of bones completely involved in Paget's disease the total mineral content does not approximate that originally present. Deviation from the normal in the chemical composition of such bones has been described, but there are few observations available. The softness and bending of the bone show that it is statically inferior. The main reason for the softness is the reduced calcium content. The firmness of the bone is not much increased except when sclerosis appears, and then the bone may become brittle. The sclerosis is not uniform, and while sclerotic patches may be present in some areas of a bone or the sclerosis may involve an entire bone, other bones in the same case may show no sclerosis. A sclerotic bone may be heavier than it was before the disease set in; sclerosis is a healing process.

Fractures (complete) are not so rare as the literature seems to indicate; the tibia and femur are the bones most easily fractured. Fracture occurs often after slight trauma, and may sometimes appear spontaneously. Fractures may heal completely, though possibly somewhat more slowly than normally. Definite evidence of callus may be found on roentgen examination, generally during the sixth to eighth week, though in a patient observed at this hospital a large callus was seen 4 weeks after fracture of the femur. However, callus formation may be delayed. As the callus goes through the various stages of calcification and ossification it becomes involved in the pathologic process, and the new bone also shows roentgen evidences of Paget's disease.

The fracture may be an incomplete fissure, which may become complete with slight trauma. Figure 7 shows a partly curved tibia, with many distinct fissures and many more that are rather indistinct. At the junction of the upper and middle thirds of the bone, one of these fissures runs rather irregularly entirely through the thickness of the bone, producing a complete fissure fracture. It is clear that slight trauma to a bone with such a fissure may lead to wide separation of the fragments. Salinger [28] seems to be the first to point this out roentgenologically; he interpreted these ribbon-like zones of increased transparency as Looser's transformation zones. Looser [29] had described such clear transverse zones in osteomalacia and late rickets, and believed that in the latter diseases the clear transverse zones resulted from the substitution of poorly calcified bone or osteoid tissue for normal bone. He therefore eliminated the factor of fracture as the cause of the *Aufhellungszonen*.

On histologic examination Schmorl concluded that the clear transverse zones in deformed Paget bones were fissures.[7c] When examined

28. Salinger, H.: Fortschr. a. d. Geb. d. Röntgenstrahlen **39**:1049, 1929.

29. Looser, E.: Deutsche Ztschr. f. Chir. **152**:210, 1920.

histologically, these fissures have toothlike borders and extend transversely through the diseased cortex. Reactive tissue in or about the fissures is found only exceptionally, the inference being that they are usually rapidly filled in, and only those are observed that are sustained immediately before death. Thus, it is possible that the clear zones observed roentgenologically in a number of diseases are not results of the same pathologic process. Hemorrhage observed by Schmorl in the

Fig. 7.—Roentgenograph showing numerous incomplete fissure fractures in a curved tibia; at the junction of the upper and middle thirds of this bone, one of these fissures runs rather irregularly through the entire thickness of the bone.

immediate vicinity of the edges of a fissure suggests a fractured etiology. The conditions under which the fissures appear in Paget's disease are not known, but they may have a traumatic genesis. The filling in and healing, and the possibility of repetition of this occurrence, have led to the assumption that fissures are at the basis of the increase in length of deformed tubular bones.[7e]

The pathologic changes in other organs and tissues are not specific. In uncomplicated cases they are those usually associated with aging, with the frequent featuring of cardiovascular degeneration. Changes in the parathyroid glands have been described and alleged to be important. Slight degrees of hypertrophy, especially of the main glands, may occur, and this is secondary to the underlying pathologic changes in the bones. A large parathyroid adenoma has been occasionally described in association with Paget's disease. No such examples have been described in the literature since 1925, when parathyroid adenomas were definitely recognized as playing a rôle in the pathogenesis of von Recklinghausen's disease. One of the first descriptions of the presence of an enlarged parathyroid adenoma in association with bone diseases was by Askanazy.[30] His case was classified as osteitis deformans without osteoid. Close reading of his report shows that he was dealing with generalized osteitis fibrosa and not with Paget's disease. The conditions in which parathyroid adenomas have been described were probably incorrectly classed as Paget's disease.[30a]

MICROSCOPIC ANATOMY

One of the strongest claims entitling Paget's disease to consideration as an entity resides in the peculiarity of several of its histologic

30. Askanazy, M.: Arb. a. d. Geb. d. path. Anat. Inst. zu Tübingen **4**:398, 1904.

30a. Since this paper was submitted, autopsy has been performed in the case of W. T. (admission 39124). The vertebrae, the sacrum and the upper portion of the coccyx presented extensive changes; a number of the vertebral bodies showed reduction in their superior-inferior measurements and increase in their anterior-posterior measurements. The intervertebral disks were for the most part in fairly good condition, and when this was the case, their nuclei were obviously markedly turgid, their substance springing forward actively from the cut surface; some of the disks were thinned considerably, while others showed an apparent prolapse of the disk substance into the vertebral bodies. The fourth lumbar disk had markedly increased its anterior-posterior diameter at the expense of the spinal canal, which it partially obliterated. It is striking that, in spite of the extensive involvement of the entire spine, there was no deformity, except for a slight degree of lateral curvature in the lumbar regions, noted at the autopsy table. The flexibility of the dorsal spine was considerably impaired by an ankylosing spondylitis, which was undoubtedly a factor in preventing curvature. The pelvic bones, sternum, left clavicle, left femur, left tibia, right tibia, fibulae, patellae, right humerus and right scapula were examined and showed varying degrees of Paget's disease. The bones of the left foot were removed (except some of the phalanges), and the calcis was the only one that on section showed definite gross implication by Paget's disease. Of the ribs studied, only the first was diseased. The calvarium was irregularly thickened, and some portions of the parietal bone seemed not at all thickened or transformed, as both the inner and outer plates were present; in the frontal region, some degree of sclerosis was seen. The parathyroid glands were not abnormal. The blood vessels showed considerable arteriosclerosis.

features. While its striking appearance had been noted long ago (having originally been touched on by Butlin in his contribution to Paget's first paper [1]), to Schmorl must be conceded the credit of bringing into relief the rather specialized histologic appearance of this bone disease. According to Schmorl, completely and typically developed Paget's bone is found on histologic examination to consist of irregular segments of lamellar bone (*Breccie*), which are separated by short, irregular and often somewhat toothed cement lines. Freund, furthermore, emphasized that these cement lines stain much more deeply than normally when dyed with hematoxylin, and that they are both very short and numerous. Thus, an area of bone totally transformed and completely involved by Paget's disease consists, microscopically, of tiny fragments of lamellar bone fitted into one another like a very irregular mosaic, with little tendency for the bone fragments (as pointed out by Freund) to be arranged about vessel canals to form haversian systems.[31]

Moreover, Knaggs, about the same time and entirely independently, commented on this striking histologic feature of the pathologic picture of Paget's disease, describing the bone as "decorated with internal curvilinear markings." [21] He also gave photomicrographs which leave no doubt that his observations in this regard were along the same lines as those of Schmorl.

As stated, the typical mosaic architecture is to be found only in completely developed Paget's bone. Thus, on examination of bones in a case of Paget's disease, this architecture is not necessarily evident throughout. If any of the original cortical or spongy bone still exists, it will not show the irregular mosaic architecture; nor do such pictures occur in the connective tissue bone that appears in the marrow during the evolution of the pathologic process.

The mosaic architecture comes into existence as the result of a complicated cycle of bone resorption and apposition. This cycle affects both the original compact and spongy bone and the new-formed connective tissue bone. They are subjected to rapid and continuous resorption and apposition, each new encroachment on the bone that is being resorbed leaving a resorption line, part or all of which remains as a cement line when the new bone is deposited. These irregular cement lines, with the intervening fragments of bone, create the mosaic architecture. Thus, the mosaic appearance is an expression of the fundamental processes underlying the transformation of the original lamellar bone or the new-formed connective tissue bone into Paget's bone. Whether the resorption and apposition are precipitous—that is, whether

31. It is essential in preparing bones presenting Paget's disease for microscopic examination to fix them in formaldehyde and embed them in celloidin. The use of chromate fixatives is distinctly contraindicated.

they occur in rapid succession—cannot be answered with certainty, but some of the histologic features suggest this. Sometimes resorption is so progressive that mosaic structures do not form, especially, as Schmorl pointed out, in functionally active areas. If this is the case, large quantities of connective tissue bone appear in the rich vascular fibrous marrow that replaces the original bone.

Until recently it was supposed that fibrous transformation of the bone marrow was the initial and primary basis for the pathologic changes in this disease. Many facts seem to challenge such a view. It is, of course, true that extensive fibrous transformation of the marrow occurs in other bone diseases without the rather distinctive picture of Paget's bone appearing. It seems likewise to be the case that the connective tissue transformation of the marrow is a secondary change in Paget's disease, and Schmorl is probably correct in giving it the same significance as the transformation of normal marrow into fibrous marrow, as it occurs in rickets and osteomalacia. In these diseases the marrow changes are believed to follow in the wake of mechanical and functional needs.

Several photomicrographs are included to illustrate the features of the microscopic anatomy so far discussed. Figure 8 *A* shows the transformed, mosaic appearance of fully developed Paget's bone; the variously sized fragments of lamellar bone are separated by wide, blue-staining cement lines, which are in some places straight and in other places so irregular as to produce a pronounced scallop. The small, irregular fragments of bone appear like so many pieces of atypical interstitial lamellae, and the vessel canals are not surrounded by thick zones of concentric lamellae to create an osteon.[32] The vessel spaces are filled with a loosely cellular, edematous, and quite vascular connective tissue which contains a sprinkling of infiltrating cells, many of which are lymphocytes and plasma cells. Narrow zones of newly deposited bone may be observed on the surface about the vessel canals.

The connective tissue bone that appears in Paget's disease, although it is rather fine-fibered, does not show the mosaic. Figure 8 *B* is illustrative of this fact. The photomicrograph shows some subchondral connective tissue bone from the head of the femur in my case. The rather thick trabebulae of connective tissue bone are lined by osteoblasts, and the intervening connective tissue stroma is quite cellular and shows a moderate number of osteoclasts in lacunae on the bone surfaces. When this connective tissue bone is resorbed and transformed into lamellar bone, and when resorption and deposition have repeatedly occurred, the mosaic appearance with scalloped cement lines is created. The marrow, under such circumstances, tends to become less

32. Jaffe, H. L.: Arch. Surg. **19**:24, 1929.

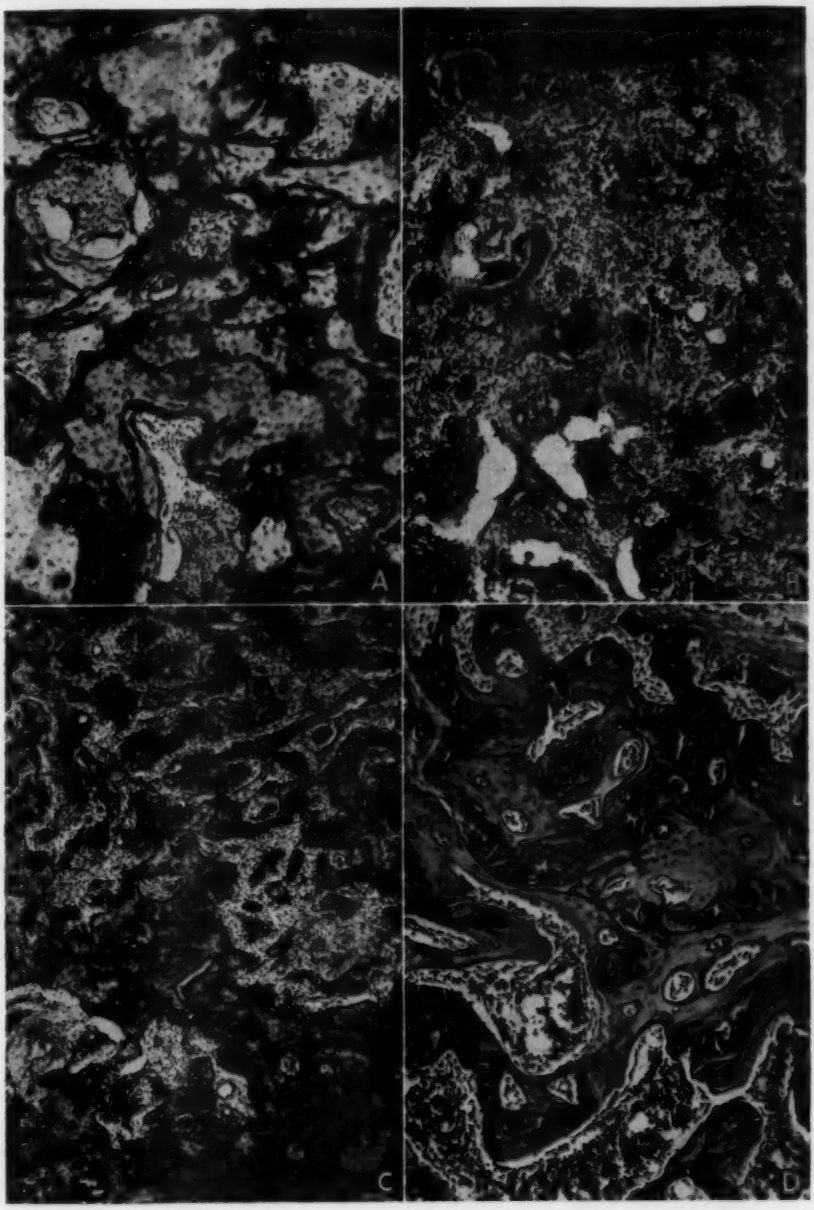

Fig. 8.—Photomicrographs: *A*, bone with fully developed Paget's disease, showing the typical mosaic appearance of such bone; × 65. The variously sized fragments of lamellar bone are separated by wide cement lines. Note the complete absence of typical haversian systems. *B*, subchondral connective tissue bone; the mosaic appearance is absent; × 65. *C*, lowermost portion, lamellar bone with the mosaic architecture; uppermost portion, gradual evolution of such bone; × 35. *D*, cross-section of an experimental rat tibia with numerous cement lines creating a suggestive, but not typical, mosaic architecture; × 115.

fibrous and more fatty, and the number of osteoclasts observed in the stroma becomes less. These features are shown in figure 8 *C*.

The histologic description of the evolution of Paget's bone given does not take into consideration the bizarre appearances in Paget's bone that baffle explanation. Hematoxylin reveals great irregularity in the stainability of the bony tissue, and irregular segments are observed that tend to stain blue as if their calcium content were different from that of the rest of the bone. This is not the only baffling feature, for in such areas the nuclei are not arranged in as parallel formation as they are in normal lamellar bone. One gets the impression that in the progressive changes, with their mutual interactions (which may fail to go on to the final stage in some sections), islands of incompletely transformed connective tissue bone become included between portions of lamellar bone and show up as irregular, bluish-staining areas. This seems to be especially the case during the active phases of the formation of Paget's bone, when there must be accelerated vicious and incomplete resorption and deposition. Such bluish-staining areas are also seen in Paget's bone undergoing degeneration.

Mosaic pictures are not encountered in conditions other than Paget's disease with any degree of regularity or frequency. The chaotic architecture is sometimes observed in generalized osteitis fibrosa cystica (von Recklinghausen's disease), but it does not show the great irregularity of the cement lines so prominently associated with Paget's bone. In generalized osteitis fibrosa cystica, the peculiar internal tracery is present especially about the cysts and brown tumors. Jaffe, Bodansky and Blair [6d] demonstrated this to be the case in chronic experimental hyperparathyroidism; the bone frequently contained numerous cement lines, although these were fairly regular. This was especially true when the animals were subjected to repeated interruption of the injections of parathyroid.

The mosaic architecture is not observed in focal fibrous bone lesions, or in the bone about solitary bone cysts. Pick [20] described such pictures in the new bone formed during the early stages of syphilitic hyperostoses. They may also be seen focally, as, for instance, in the bone about intervertebral disk extensions into the bodies of the vertebrae, or in accessory scaphoids which have been subjected to constant pressure and trauma. Thus, when mosaics appear in conditions other than Paget's disease, their extent is limited, and the cement lines tend to be more regular.

The mosaic architecture which is more or less specific for Paget's disease reflects the underlying pathologic processes. It plainly points to the facts that in Paget's disease there exists a great capacity for new bone formation, with an almost greater capacity for resorption of new

and old bone, and a particular ability of the newly formed bone to become rapidly transformed into adult bone. Thus, if experimental conditions are created which permit the fulfilment of the conditions enumerated, which seem essential to the production of the mosaic architecture, one may expect to produce in the experimental animal microscopic pictures simulating, although not exactly, the histologic picture of Paget's disease. Suggestive pictures were created by Jaffe, Bodansky and Chandler [33] in rats fed a diet insuring a high intake of calcium and given elementary phosphorus and injections of parathyroid extract. The stimulating effect of small doses of elementary phosphorus on endosteal, periosteal and endochondral bone formation had been demonstrated by Wegner, and we expected that with a high intake of calcium and the dosage of parathyroid extract conditions for a vicious cycle of bone resorption and deposition would be created. The irregular mosaic picture experimentally produced in our animals, though not typical of Paget's disease, suggests some of its features (fig. 8 *D*).

Since Paget's disease so frequently involves the vertebrae, microscopic examination of such bone in the florid stage shows practically all features of the histologic evolution: active resorption of the original spongy trabeculae with osteoclasts within Howship's lacunae may still be seen in some areas; new bone deposited on the resorption surfaces of such trabeculae by way of repair will then also be observed; in other areas, more advanced resorption of the original and also of part of the newly formed bone leads to an increase in the marrow connective tissue; the marrow changes in still other regions will be seen to have taken on considerable proportions, and they become important for the formation of the large amounts of connective tissue new bone which become a feature of the microscopic picture. The greater the celerity and degree of the resorption, the greater the degree of marrow fibrosis. When the marrow connective tissue forms bone, resorptive processes set in, and such resorption is the incentive for the proliferation of additional marrow connective tissue. In the meantime, portions of the earliest formed connective tissue bone become transformed into lamellar bone and are delineated from the more recently deposited bone by wide, irregularly curved cement lines, creating the mosaic architecture. When the lesion is sufficiently advanced, low power examination of a large field of a vertebral body shows that the newly formed spongy Paget's bone now appears as a thick, coarse-meshed, trabecular formation in various stages of growth (fig. 1 *B*). These trabeculae are irregularly bordered and separated by tracts of connective tissue of variable widths and show the mosaic architecture.

33. Jaffe, H. L.; Bodansky, A., and Chandler, J. P.: Unpublished studies.

Using the irregular mosaic or chaotic architecture as his criterion, Schmorl stated that he was able to diagnose even the beginning stages of Paget's disease. These earliest stages were observed only 4 times in his large material (twice in the sacrum and twice in the lumbar vertebrae).[7e]. The early changes, according to him, are recognized with difficulty, and they are usually limited to small areas in the subchondral spongiosa: Gross examination reveals small foci consisting of a few more or less thickened, lusterless-white trabeculae, which may show toothlike processes. On microscopic examination, such areas reveal some normal-appearing trabeculae the surfaces of which are lined by osteoblasts and osteoclasts, while adjacent to them may be trabeculae with the mosaic architecture resulting from the wide irregular cement lines. The surfaces of these trabeculae are lined by osteoblasts and osteoclasts, while the intertrabecular marrow remains myeloid with moderate amounts of fat cells. All indications are to the effect that a transformation of bone is occurring. Even in larger foci, in early stages of the disease, fibrous transformation of the marrow seems limited to the neighborhood of greatly deformed trabeculae.

As has been indicated, observation of the beginning stages of Paget's disease is rare. One cannot be overly cautious, therefore, in interpreting the significance of tiny foci of thickened trabeculae in the vertebrae, where the trabeculae are ordinarily thin and of more or less uniform appearance. The significance of such tiny foci showing the mosaic architecture, in the absence of evident gross involvement in the other bones, remains to be elucidated. The important question to be answered is: Does the presence in these bones of a number of such foci constitute sufficient reason for making an anatomic diagnosis of Paget's disease in the absence of clearer indications in other bones? It is known that a lesion must reach certain quantitative proportions before it is capable of producing a characteristic disease picture. It seems that an analogy may be drawn from renal pathology. It is rather unusual to observe a kidney from a person past middle age without finding a number of sclerosed and hyalinized glomeruli, predicated on a vascular injury. Only when a glomerular hyalinization becomes fairly marked and interstitial connective tissue overgrowth pronounced, does the lesion become one that is designated as primary contracted kidney. Therefore, it seems the better part of discretion to withhold a diagnosis of Paget's disease in cases showing only such foci in the vertebrae until the focal lesions are clearly shown to be associated in a sufficient proportion of cases with simultaneous involvement of other bones to justify the acceptance of their significance for an independent diagnosis.

In regard to long tubular bones, and especially as concerns the cortex, it is much more difficult to trace the evolution of the disease.

Schmorl found that in an apparently normal portion of the cortex of a tubular bone, several centimeters from an obviously involved area, the earliest evidences of cortical involvement may be observed. He describes the first change as manifested by the appearance of osteoclasts lying in Howship's lacunae in some of the vessel canals of such a cortical area; at this stage, the other contents of the canals are not changed —they contain fibrillar material, fat cells and a few myeloid cells. As the canals enlarge, more osteoclasts and blood vessels appear, and the resorption spaces which are enlarged are only separated by thin layers of bone. Finally, the adjacent enlarged canals fuse, and the marrow content becomes much richer in spindle cell connective tissue. As yet there is little new bone formation on the bony surfaces of the enlarged spaces, but with the appearance of bone in the proliferated marrow connective tissue, some of this newly formed connective tissue bone becomes deposited on the walls of the enlarged spaces. Osteoblasts line the surfaces of such bone newly deposited on the irregularly resorbed bony walls of the spaces, and also on the trabeculae of newly formed bone in the osteogenic marrow. The resorption and reconstruction of the new and old bone, which now become very active, follow the same steps as were described in discussing the vertebrae and in portraying the evolution of the mosaic architecture. Finally the reconstructed bone shows a histologic picture entirely similar to that in the newly formed spongy trabeculae of a vertebra transformed by Paget's disease.[7e]

From these findings one may infer that the disease so far as the cortex is concerned is initiated in the haversian canals and not in the major marrow cavity. The changes progress to the periosteal and endosteal surfaces of the cortex. If the disease is arrested at this stage (when cortical transformation had become completed), the cortex may not thicken especially, and the major marrow cavity will not change in diameter. Under such circumstances, the inner and outer ground lamellae are not reconstructed, and the histologic picture shows a compacta that is completely transformed into Paget's bone. The outer ground lamellae are still present and may be of normal thickness, and rudiments of the inner ground lamellae may be observed as under normal conditions. Such bone is traversed by numerous, more or less regularly disposed spaces, which are irregular in form and width. They are filled with fatty or fibrillar marrow and contain sprinklings of myeloid cells. The bone between the spaces shows the mosaic architecture, but typical haversian canals and spaces are absent. The loose connective tissue between the new-formed trabecular framework contains numerous thin-walled capillaries and dilated lymph spaces. Figure 9 *A* is a low power photomicrograph showing the general architecture of cortical bone so transformed.

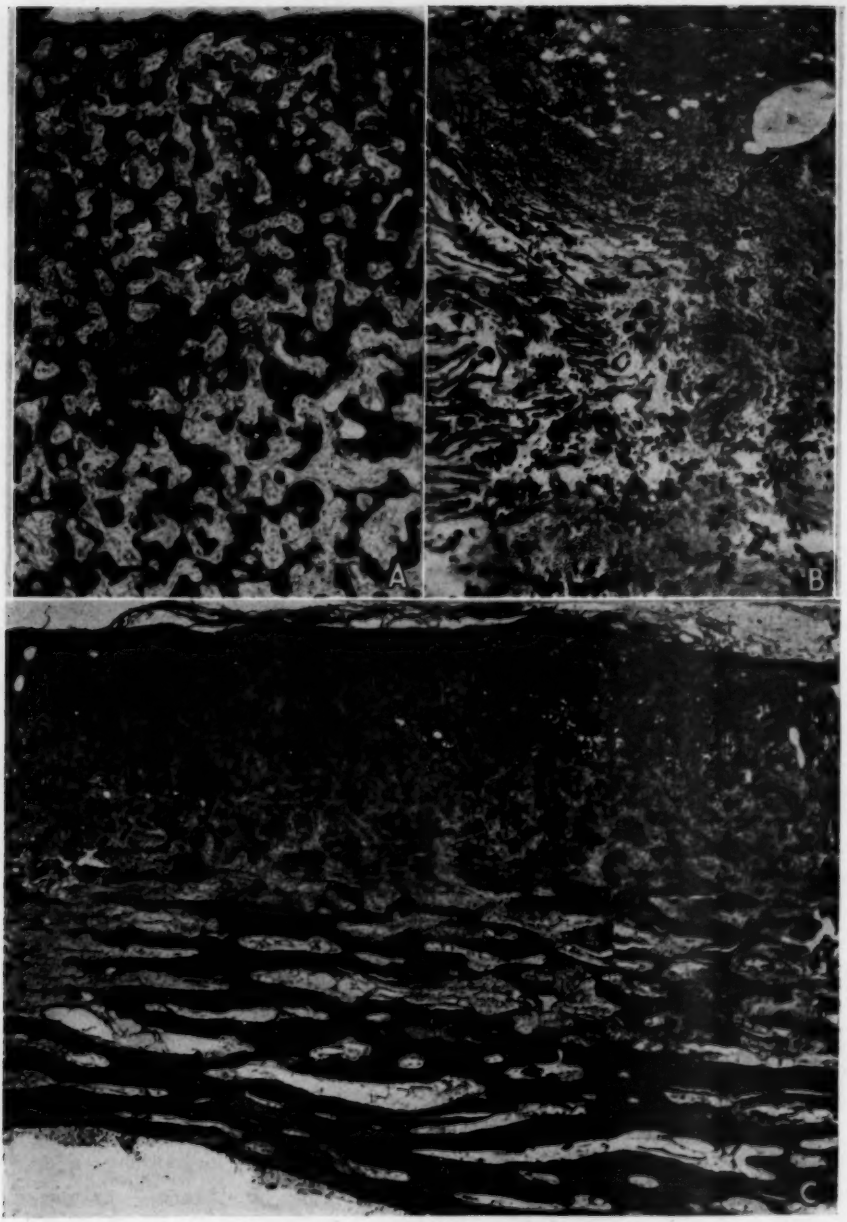

Fig. 9.—*A*, low power photomicrograph showing the general architecture of compact bone transformed into Paget's bone. The outer ground lamellae are still present, and such bone is traversed by numerous more or less regularly disposed spaces; the bone between these spaces shows the mosaic architecture; × 10. *B*, photomicrograph of some of the fatty marrow removed from the major medullary cavity (fig. 3). The free hemorrhage and the large pigment-containing phagocytes are clearly seen; × 115. *C*, periosteal bone from the region marked *X* in figure 3. The thick layer of periosteally formed connective tissue bone is most primitive superficially, but becomes transformed into Paget's bone more deeply. The transformed deeper lamellated Paget's bone clearly shows the mosaic architecture; × 7.

The appearance described pertains to the typical picture, and naturally there are considerable variations dependent on many other factors. For some unknown reason the numerous cells within the loose connective tissue may be polymorphonuclear leukocytes, many of which are eosinophils. Sometimes considerable amounts of blood pigment are observed in this loose connective tissue, accompanied by phagocytes containing such pigments.

The number of osteoclasts seen in any section varies with the stage of the disease and with its activity, the amount of transformation that is in progress and the factor of healing. They may be numerous, but only when the stages of active destruction and transformation are most marked. They are scavengers removing the decalcified bone.[34] When numerous, as many may be seen as in the lesions of von Recklinghausen's disease. During the regression or stages of stability, large areas of bone may be observed without more than an occasional osteoclast.

When the disease progresses to transform the entire cortex, and then continues, periosteal proliferation is stimulated and resorption on the medullary side occurs. Periosteal proliferation is obvious grossly, as has been indicated, especially in cases which are complicated by fracture. Freund's [22] detailed discussion of the part played by the periosteum was the first to settle this question completely. Schmorl described 2 types of periosteal thickening—one by the formation of an increased number of periosteal ground lamellae, and the second by proliferation from the cambium layer of the periosteum (connective tissue bone formamation). In the first type, fine, parallel-fibered bone is deposited on the compacta, and this becomes transformed into Paget's bone. This type of periosteal proliferation is not common and never extensive. The second form, in which there arise thick deposits of connective tissue bone from the periosteum, which rapidly become transformed into Paget's bone and fused with the rest of the cortical bone, is the more usual. Such periosteally formed bone is at first quite primitive, and the intertrabecular marrow is traversed by numerous vessels, which give this bone the reddish color observed on gross examination and which account for its pumice-like appearance. Usually only small amounts are observed at any one time, as it becomes rapidly transformed into Paget's bone, so that the periosteal proliferation may be missed. This explains why periosteal proliferation was not generally recognized until recently.

Rarely, the periosteal proliferation may be sharply and easily discerned with the naked eye, as described under "Gross Anatomy," and may reach a thickness of several millimeters. This is demonstrated in

34. Jaffe, H. L.: Arch. Surg. **20**:355, 1930.

figure 9 *C*, from my own case, which shows a thick layer of periosteally formed connective tissue bone, most primitive superficially, but becoming transformed into Paget's bone more deeply, where it fuses with the Paget-transformed, original cortex.

On the marrow side, new bone formation is seldom seen, and when it occurs it is probably mainly on the basis of connective tissue new bone formation. When it forms, it is generally rapidly resorbed. In fact, the usual feature of Paget's disease is a slow, progressive resorption from the endosteal side, which leads to the production of a markedly irregular endosteal surface, so plainly seen in the macerated specimen shown in figure 3.

Freund has described the innermost zone of the transformed compacta as consisting histologically of very delicate (filigree) trabeculae. The cross-sections of the femur in my case show such trabeculae, and Schmorl has also observed them, but only in cases in which there was a complicating osteoporosis. He found that the greater the degree of osteoporosis, the more delicate were these inner trabeculae. Conversely, he remarked that the trabeculae are thickest in those cases in which Paget's disease is active to the time of death.

The marrow contained in the major cavity of a long tubular bone is likely to undergo a great number of changes. On the whole, it is fatty. Numerous areas of hemorrhage may appear in it, which result in the appearance of large numbers of pigmented phagocytes and fibrillar connective tissue in the course of organization. In such areas, some new-formed connective tissue bone trabeculae also appear. Islands of myeloid marrow remain scattered throughout the fatty marrow (fig. 9 *B*).

Extensive areas of anemic or hemorrhagic necrosis may result in the death of large areas of intertrabecular marrow and the contained bone. Liquefaction may evoke the infiltration of large numbers of inflammatory and phagocytic cells, and fat-containing scavengers may also appear in such areas. The end-result, naturally, will be liquefaction with the formation of cystic spaces, which have been described as frequent gross features of the disease. The microscopic appearance of such areas in the course of the formation of cystic spaces may be observed in figure 10.

Paget's disease shows a great natural inclination to spontaneous healing, and the histologic examination frequently discloses evidences of this process. Florid and healing processes may be observed in different bones of the same subject, and even within the same bone. The recession of the amount of connective tissue is part of the healing process, this tissue disappearing to a great degree in the bones that are healing. The fibrous marrow becomes replaced by more lymphoid and fatty marrow.

Complete healing is associated with a tendency to the return of a normal appearance of both the bone and marrow. However, the picture resulting from the presence of the numerous irregular cement lines may persist in healing lesions, possibly for years. In experimental animals, when the cement lines become irregular, the appearance persists for some time after the experiment is interrupted, and the bone

Fig. 10.—Photomicrograph of section cut through the region marked *X* in figure 3, showing a cystic space in the cortex, the result of degeneration and liquefaction of bone between the already formed Paget's bone and the periosteally formed new bone; × 6.

does not appear completely normal until the slow process of creeping replacement has led to reconstruction. It is held that considerable healing may take place even in disseminated Paget's disease. As part of the healing process, the bones tend to become sclerotic and even eburnated.

Healing is associated with an attempt to reconstruct a more compact bone. As a result, lamellar bone formation on a more normal basis appears on the walls of the enlarged vessel canals; these become progressively reduced in size. The vessel spaces become lined by osteoblasts and lymphoid marrow reappears in these spaces; this is most prominent in the diploic spaces of the skull. This healing process may be diagnosed histologically, since considerable reduction of the chaotic architecture occurs. The cement lines become more regular and thinner, and the inclusion masses disappear, probably by the process of creeping replacement. It has been held that healing chronic osteomyelitis may occasionally produce a histologic picture suggestive of Paget's disease. This belief is probably based more on roentgen findings than on microscopic studies, for these do not support such a view. In a large experience with healing chronic osteomyelitis nothing was observed to indicate more than the most casual similarity in the histologic processes.

SARCOMA COMPLICATING PAGET'S DISEASE

Bird,[35] consulting the records of four large Boston hospitals, found that of 64 recorded cases (all polyostotic), 7 had been complicated by bone sarcoma. In 5 cases the diagnosis was verified by biopsy or autopsy. Because of this rather high incidence, 1 in about every 10 cases of disseminated disease, he suggested that any elderly person affected with a bone sarcoma should have x-ray pictures of the rest of the skeleton with the view of ruling out Paget's disease. In 3 of his cases, the sarcoma seemed to have developed definitely as a complication of a preexisting Paget's disease. Speiser,[36] collecting material from another source, stated that in 6 of approximately 150 cases of disseminated Paget's disease the bones had undergone sarcomatous degeneration. During the last 4 years, 2 instances of sarcoma complicating Paget's disease, both terminating fatally, came under my attention.

Breslich [37] recently collected from the literature 22 instances of sarcoma involving bones affected by Paget's diseases. Nineteen of these occurred in men and three in women. The ages of the patients ranged from 36 to 72 years; the average age was about 55. The time elapsing between the onset of Paget's disease and the appearance of the sarcoma was frequently unknown, but in 7 of 12 patients, Paget's disease was not suspected until it was demonstrated by roentgen changes.

35. Bird, C. E.: Arch. Surg. **14**:1187, 1927.

36. Speiser, F.: Arch. f. klin. Chir. **149**:274, 1927.

37. Breslich, P. J.: Arch. Surg. **23**:813, 1931.

Approaching the problem from another angle, Coley and Sharp [38] collected from Memorial Hospital and the Registry of the American College of Surgeons 71 cases of osteogenic sarcoma in patients over 50 years of age, and in 28 per cent Paget's disease was found associated with the sarcoma. From their statistical study they concluded that when osteogenic sarcoma is associated with Paget's disease, it invariably develops in a bone showing the characteristic changes of Paget's disease rather than in an otherwise normal bone. It should be noted that their deductions in regard to the co-existence of Paget's disease are based entirely on roentgenologic examinations; actually only few instances of Paget's disease so complicated have been reported in which complete skeletal examination was made.

The point that should be recognized is that these sarcomatous complications are reported to occur in advanced cases with disseminated bone involvement. Since many uncomplicated cases of Paget's disease are not reported, it is difficult to estimate accurately the frequency of this complication. The sarcomatous foci are often widely disseminated, with multiple foci in the involved bones, as the roentgenogram of a skull in figure 11 clearly shows; this represents a case of Paget's disease with sarcoma that came to my attention and in which a biopsy specimen from a focus in the tibia was obtained.

The histologic picture of the sarcoma in Paget's disease differs from that frequently seen in uncomplicated osteogenic sarcoma. The multiple foci of involvement suggest the possibility that the sarcomas complicating Paget's disease arise simultaneously or at closely related intervals in a number of different bones undergoing malignant degeneration. Gruner, Scrimger and Foster [39] stated that the chief difference histologically between the tumor and the fibrous tissue between the trabeculae is the apparent unrestrained growth of the former; the tumor growth being added to a tissue already osteoblastic. Von Albertini [40] reported that in his case the marrow of bones affected by Paget's disease only was in many places converted into a cellular sarcoma-like (presarcomatous) tissue, composed of large spindle cells. This cellular tissue did not invade or destroy the surrounding structures, and he considered it an intermediate stage between the chronically inflamed fibrous marrow and the polymorphocellular tumor observed in those portions of the bone showing sarcoma. He, however, clearly indicated that he did not consider the ordinary marrow reaction of Paget's disease as presarcomatous.[41] The tumors observed by Bird [35]

38. Coley, B. L., and Sharp, G. S.: Arch. Surg. **23**:918, 1931.

39. Gruner, O. C.; Scrimger, F. A. C., and Foster, L. S.: Arch. Int. Med. **9**:641, 1912.

40. von Albertini, A.: Virchows Arch. f. path. Anat. **268**:259, 1928.

41. von Albertini, A.: Fortschr. a. d. Geb. d. Röntgenstrahlen **41**:443, 1929.

were fibrosarcomas. In a case observed by myself, the sarcoma showed a rather complicated morphology. Certain areas were rather typical of a very cellular fibrosarcoma, while in other areas the tumor cells were swollen and polyhedral. Great numbers of tumor giant cells and numer-

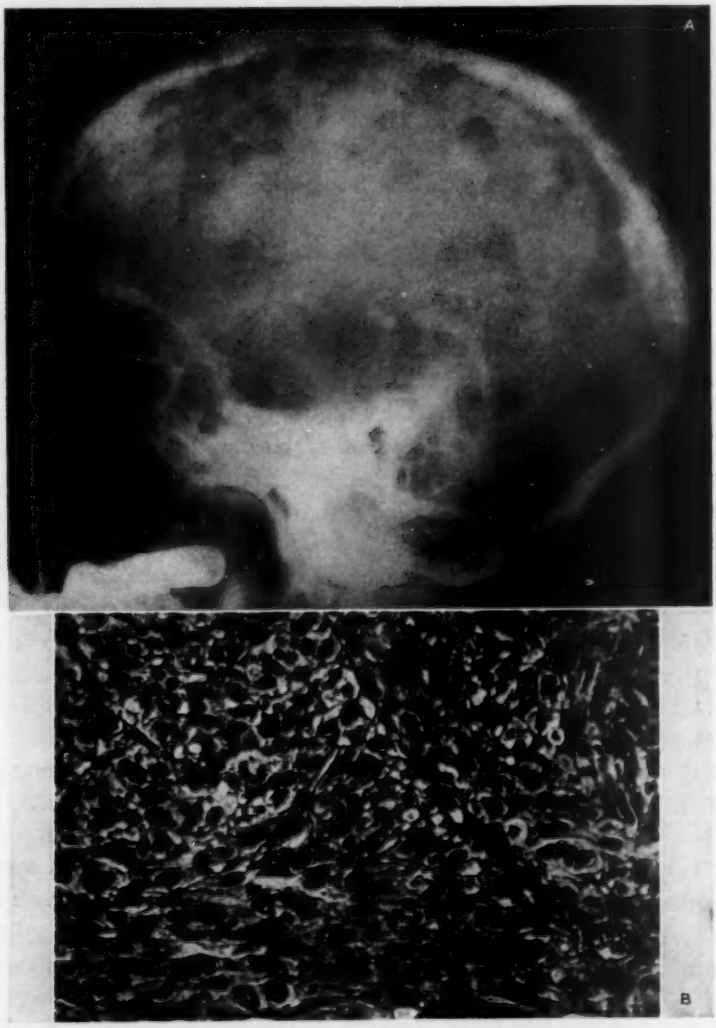

Fig. 11.—Above, a roentgenograph of the skull of a patient with Paget's disease, showing multiple sarcomatous foci. Multiple sarcomatous foci were also found in other regions of the skeleton. Below, a photomicrograph of an area in tumor tissue removed from the tibia of the patient whose skull is shown. The very cellular appearance and complicated morphology are evident; × 300.

ous mitoses were present. The intercellular material was scant, and there was no calcification or ossification of the tumor. This dis-

tinguishes the lesion from the ordinary run of so-called osteogenic sarcomas of bone, and whether the absence of calcification or ossification is related to the rapid growth requires consideration (fig. 11, photomicrograph).

To deny an important causal relationship between polyostotic Paget's disease and the sarcoma that may complicate its course would seem to be incorrect, and to blind one to what certainly appears to be a feature of great significance. In dealing with this phase of Paget's disease, one is confronted with a problem that is of the utmost importance in elucidating a phase of the basic pathologic reaction. The tendency to sarcomatous complication sets Paget's disease off from the other dystrophic bone diseases. The connective tissue proliferation in this disease may from the beginning have a different relationship to the disease process than the connective tissue overgrowth in other dystrophic bone disease has to those diseases. The sarcoma seems to stand in a relationship to the marrow connective tissue similar to that of a fibrosarcoma of the uterus to the original fibroid. The initiating cause of the tumor formation is not clear, but trauma, fracture and chronic inflammation have been suggested. It is, however, quite likely that the tremendous proliferative capacity of the tissues involved in polyostotic Paget's disease may of itself be the basic stimulus to tumor formation.

CLINICAL PHASES

The clinical picture of the case in which many bones are involved was so clearly drawn by Paget [1] that in succeeding time little has been added thereto. He recognized that the disease was slow in progress, and could continue for many years without seriously influencing the general health of the patient; he observed that the tubular bones in such cases thicken, soften, bend and elongate, and that those bearing weight may become badly misshapen. Bending of the long tubular bones in such cases is first seen, and is nearly always most noticeable, in the lower extremities. The limbs, however, remain strong enough to support the trunk even in the most advanced stages of the disease. In this respect, polyostotic Paget's disease differs from advanced osteomalacia, osteoporosis and generalized osteitis fibrosa cystica. When many bones are affected, some may appear at any stage to be only partially involved, but the lesion may gradually extend to the whole bone. In the legs or forearms, if a single bone is affected, it may assume a curved form between 2 fixed points. It is indeed very curious that the fibula is rarely, if ever, involved.

The curved lower extremities show a convexity toward the outside, so that the patient becomes bowlegged. Besides the lateral convexity, there frequently is an anterior convexity of the tibia, resulting

in the so-called saber-blade form of tibia. The neck of the femur is bent horizontally and frequently forms a right angle with the shaft of the bone, making the trochanter jut out further than normally—coxa vara. The pelvis may become markedly deformed. In some cases, however, the course of the bone deformities does not follow the usual pattern. Clutton [42] recorded the case of a woman in whom, although the usual bones were affected, the disease reached its greatest severity in the right radius. Others also have noted deviation from the usual course of the disease when it progresses to the polyostotic form. In the vertebral column, curvatures may occur which, with changes in the thorax, may give rise to circulatory and respiratory embarrassment. The changes in the vertebral column, femora and tibiae often result in a considerable reduction of the subject's height, which, with the low-set, protruding head, hanging and seemingly lengthened arms, pendulous abdomen, bowlegs, bent carriage and waddling gait, gives a certain apelike appearance to the patient with multiple bone involvement.

In its first years, and sometimes throughout its course, the disease is usually attended with pain in the affected bones. This may be marked long before alteration in their appearance can be detected clinically, and when present may continue during the progress of the bone changes, varying in intensity, sometimes disappearing entirely. There is nothing specific about the pain as a symptom; pain accompanies numerous other generalized bone diseases, such as osteoporosis, generalized osteitis fibrosa cystica and osteomalacia, and may be more severe in the latter. In some cases, pain is not present, or is insufficient to attract attention. Hurwitz [16] has described 2 such cases, in which the disease developed marked features unsuspected by the patients, who came under observation for cardiovascular symptoms. A case of Paget's disease of 20 years' duration, which I saw and to which reference was made, had no accompanying pain, though both lower extremities and the thorax were deformed.

Symptoms due to cranial nerve involvement are rare, with the exception of those related to the auditory nerve. Jenkins [43] reported 9 cases with some degree of deafness; some were badly deaf. When the cranium is much involved, the abnormality in hearing may be so severe as to suggest otosclerosis. Involvements of other cranial nerves, though rare, have been reported, as for instance, optic atrophy due to compression of the nerve in the optic foramen, and neuralgias, paralyses and disturbances in special senses due to special nerve involvement.

The rarity of mental symptoms in the polyostotic cases has also been commented on, especially since extensive alterations are present both

42. Clutton, H. H.: Tr. Path. Soc. London **46**:138, 1895.

43. Jenkins, G. J.: J. Laryng. & Otol. **38**:344, 1923.

in the external configuration of the calvarium and in the capacity and shape of the cranial cavity. The anterior-posterior diameter becomes lengthened, and the depth diminished. Cases of altered mentality of the nature of senile dementia have, however, been recorded. It is difficult to estimate how much of the mental deterioration is related to the slow brain trauma due to compression by bony elevations, and how much is due to cerebral arteriosclerosis. A recent case of Gruenthal [44] showed compression of the cerebrum and cerebellum, and partial disappearance of the Purkinje cells from the cerebellum; Bielschowsky relates this change to the effects of bone pressure.

It should be constantly borne in mind that the clinical features described relate only to the fully developed, classic case, in all respects similar to that which Wilks and Paget described. It is, however, of the utmost importance to recognize that the disease generally does not progress to the full classic clinical picture. This has been repeatedly impressed on one by roentgenologic findings, since the x-ray has been extensively used in examinations of bones. It is not a rare occurrence to find roentgenologic evidences of quite unsuspected Paget's disease in the pelvis, for instance, of a patient who has vague symptoms of pain related to the back. Such lesions have been known to show lack of any considerable progression when followed over a period of years.

Furthermore, Paget's disease may exist without there being either clinical manifestations or roentgenologic evidences. There cannot be any doubt that when minor degrees of involvement of the lower lumbar vertebrae or sacrum exist, even with a vague history of pain, roentgenologic evidences of such involvement cannot be obtained with present methods of examination. In the discussion of the pathologic anatomy, emphasis was laid on the fact that Paget's disease involves individual bones, sometimes few, less often many. It is therefore obvious why the disease may be present and even fairly well advanced in a single bone or in a few bones (especially when they are those of the vertebral column) without clinical manifestations.

However, when one of the long tubular bones, as, for instance, the tibia or femur, becomes diseased and when the other bones show apparently no involvement, the clinical picture of the so-called monostotic Paget's disease is produced. For many years these cases have been the subject of considerable discussion. One-bone or monostotic Paget's disease has been reported since Bowlby [45] described a case in 1883. The disease in his case seemed to be localized to the right femur for 10 years, and the diagnosis was based on postmortem findings. A critical analysis of the reported clinical cases of the

44. Gruenthal, E.: Ztschr. f. Neurol. **136**:656, 1931.

45. Bowlby, A. J.: Tr. Path. Soc. London **34**:192, 1883.

monostotic group shows, however, that only a small number properly belong to this group, for included among the reported cases are instances of other local bone diseases, which have been improperly classified, especially localized forms of fibrocystic disease, syphilis and forms of bone tumor (especially osteogenic sarcoma).

Most often the monostotic lesion is discovered accidentally, the condition beginning insidiously without trauma, and continuing for years without attracting the patient's attention. In such cases the involved bone, usually the tibia, is thickened and deformed and appears quite like a similar bone involved in the disseminated disease. The lesion may at first be limited to the diaphysis. Accurate and proved diagnosis of clinical monostotic Paget's disease becomes infinitely more difficult and far more open to question when it is necessary to blot out of the picture the vivid and absolutely characteristic appearance which multiple bony involvement gives the patient. Convincing histologic examinations in the present stage of knowledge of bone diseases are lacking in such cases.

Although older reports accept several clinical instances of Paget's disease affecting only a single long tubular bone as authentic,[46] the newer pathologic investigations show that such a clinical diagnosis is untenable unless an exhaustive investigation of the entire skeleton can be made. The monostotic feature seems to be nothing more than an earlier stage or protracted localization of Paget's disease in a single bone. Not long ago, I saw a woman, 67 years of age, who, for about 8 years, had had pain in and deformity of the left tibia. Recently pain developed in the right tibia, which now shows the early changes of Paget's disease. The skull in x-ray pictures appears osteoporotic in scattered areas. It may be that in these cases with the pronounced involvement of a single tubular bone other bones show subclinical lesions that develop only after a number of years. On this point there is no information. Furthermore, it is possible that the monostotic involvement is a residual manifestation of an arrested lesion. The rarity of such cases, and the fact that patients in larger cities are frequently lost sight of, are added reasons for hesitancy in accepting them as pathologic entities. From these statements it may be surmised that it has as yet not been established that the clinical monostotic involvement should be considered even as a clinical entity.

Confusion in the clinical diagnosis of such cases of Paget's disease may furthermore creep in, because, as Wilhelm [47] pointed out, the gross

46. Schirmer, K. H.: Centralbl. f. d. Grenzgeb. d. Med. u. Chir. **11**:559, 507, 687 and 719, 1908. Schlesinger, H.: Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. **6**:61, 1907; **7**:99, 1908.

47. Wilhelm, S. F.: Surg., Gynec. & Obst. **41**:624, 1925.

resemblance between the saber tibia of clinical monostotic Paget's disease and that of diffuse, nongummatous syphilis cannot be denied. The grosser morphologic similarities, such as deformities, elongation and bowing, and especially the saber blade form of tibia, are found in the affected bones of both diseases. By x-ray pictures of bone specimens Wilhelm beautifully demonstrated the marked degree to which the periosteum participates in the thickening of the bone involved by syphilis. The periosteally formed new bone of syphilis tends to remain distinct from the cortex, but in cases of long standing, others have shown, the division between periosteal and original bone may become indistinct and even completely disappear. In Paget's disease, the newly formed bone usually is quickly merged with the cortical bone, which is also involved in the disease process. In bone syphilis, the marrow cavity is more or less obliterated, being filled by a dense, newly formed bone mass, while in Paget's disease the marrow cavity is more frequently widened, and is uneven.

DIAGNOSTIC AIDS

The clinical laboratory offers little assistance in diagnosis. The only test of value is the determination of serum phosphatase. This test as applied to clinical medicine has only recently been developed. The serum phosphatase is frequently high in this disease, as was first shown by Kay,[48] who reported values up to 20 times the normal. His cases represented all stages of the disease, from those in which apparently a single bone was involved to those in which almost every bone in the body was affected. There is, according to his figures, a rough correlation between the severity of the disease and the level of the plasma phosphatase, the most severe cases all having high values and the milder cases usually, but not invariably, less high values. Additional cases should be studied with an improved method for the determination of serum phosphatase.[49] In this laboratory, Bodansky [50] found, using his method, values as high as 110 units per hundred cubic centimeters of serum in polyostotic forms in persons not over 50 years of age (normal adult values, from 1 to 3 units). He found values of from 5 to 10 units in less severely developed cases and in some polyostotic cases in patients past 60 years of age.

The high serum phosphatase in Paget's disease is not understood, but is probably associated with the active formation of bone that is part of the disease, rather than with destruction of bone, as suggested by Kay.[48] While determinations of serum phosphatase may afford

48. Kay, H. D.: J. Biol. Chem. **89**:249, 1930.
49. Bodansky, A.: Proc. Soc. Exper. Biol. & Med. **28**:760, 1931.
50. Bodansky, A.: Unpublished results.

valuable aid in diagnosis, the test is not specific, since high values have also been reported in generalized osteitis fibrosa cystica and rickets. It may, however, be observed that in Paget's disease the increase in serum phosphatase is associated with normal levels of serum calcium and phosphorus, while in rickets and in von Recklinghausen's disease, the serum phosphorus is lowered, and in the latter the serum calcium is raised. The diagnostic importance of the determination of serum phosphatase becomes definite only in conjunction with other chemical and clinical examinations. For instance, in this laboratory, in a case of severe generalized osteoporosis, we found serum calcium, phosphorus and phosphatase values similar to those in the less disseminated forms of Paget's disease cited. The increase in phosphatase would not be great enough to be of diagnostic value by itself when the clinical diagnosis is not clear.

The values for serum calcium and phosphorus in uncomplicated cases are always within the normal range.

Few studies of mineral balance have been made on patients with Paget's disease. Such studies as have been made have given inconclusive results. Da Costa, Funk, Bergheim and Hawk examined 2 cases, and Cuthbertson [51] more recently studied a case of his own and confirmed their work. He reported a definite retention of calcium, magnesium and phosphorus in the advanced stage of the disease, and believed that the proportional relation of these retained elements suggested that the new bone formed in Paget's disease is relatively richer in calcium and magnesium and poorer in phosphorus than normal bone. A negative balance in regard to sulphur was also found by Cuthbertson, and the figures for the bicarbonate reserve of the blood suggested that a very mild degree of acidosis might be present. Rabinowitch [52] in a recently published metabolic study of an advanced case of Paget's disease found retention of calcium and loss of sulphur. He excluded the possibility of a disturbance of the acid-base equilibrium as being associated with the disease. However, Snapper [53] found that the daily calcium excretion in 7 cases of Paget's disease was normal when compared with the controls studied under the same dietary conditions.

Rabinowitch furthermore concluded that interpretation of the inorganic balance is difficult; the data on calcium, magnesium and phosphorus may vary, depending on the stage, severity and extent of the disease. The negative sulphur balance, he believed, was significant and constant. Knowledge of the pathologic anatomy of this disease

51. Cuthbertson, D. P.: Glasgow M. J. **108**:218, 1927.

52. Rabinowitch, I. M.: J. Nutrition **5**:325, 1932.

53. Snapper, I.: Ann. de méd. **29**:201, 1931.

would lead one to such an inference even without metabolic studies, as the progress and the degree of the pathologic change is so variable that no constant balance findings can be expected. When the disease is not much advanced, it is possible that no changes in either mineral or sulphur metabolism would be discernible.

Piney [54] reported changes in the blood count. He observed eosinophilia and an even greater increase in the number of basophils in several cases, in each of which he counted at least 5,000 leukocytes. There was no anemia, and the total leukocyte count showed no abnormality. It is difficult to draw any inference from these findings; there have been no other extended studies.

Roentgenologic examinations are of the greatest importance for diagnosis, confirming the clinical findings in the polyostotic cases and helping even in suspected monostotic cases. Such examinations have disclosed Paget's disease in the absence of any clinical findings. Porosis is one of the first changes that appears in a bone to be transformed by Paget's disease. Roentgen studies have revealed circumscribed areas of osteoporosis as an early stage in the involvement of the calvarium. Osteosclerotic appearances may follow and eventually replace the porotic areas.[25] Other processes such as transformation of the structure with the formation of new bone and hyperostoses predominate later. Since the Paget changes may often be localized or more severe in a part of the body, for instance, the calvarium, the thorax, pelvis or extremities, the roentgen appearances may vary considerably. The disease is less commonly seen in the bones of the hands, feet and face.

The thickened trabeculae which make their appearance in the ends of the long bones are not sharply defined; they are often irregularly arranged. Fine markings ordinarily shown in the cancellous ends of long bones are replaced by coarse trabeculations that extend into the shaft for a variable distance, in some instances involving the entire bone. The cortical changes, such as porosity and thickening, are most pronounced. Often there are superficial periosteal defects. The bone, when extensively diseased, has the appearance of cotton wool and is more transparent than normal. In later stages, the new bone tends to become sclerosed, and is less permeable to the x-ray.

The periosteal changes of Paget's disease are recognized on roentgenologic examination only if the thickening is pronounced. The periosteal proliferation is especially differentiable when there is no fusion of the cortical and periosteal new-formed bone. The long bones finally lose their clearcut outline; they become curved and the thickening appears to be greatest on the convex surfaces. The joints on the whole

54. Piney, A.: J. Path. & Bact. **28**:122, 1925.

remain uninvolved, and it is rare to see noticeable irregularity of the joint surfaces. Figure 5 shows typical roentgen appearances in bone considerably involved by Paget's disease; the lighter shadow on the right is that of the periosteally formed bone.

POSSIBLE NATURE OF PAGET'S DISEASE

During the last 55 years such a variety of causes has been proposed that further speculation and suggestion as to the nature of the disease should really await some significant advance in knowledge. The causes suggested have ranged from heredity to irritation, and from disturbances of the endocrine glands and vitamin deficiency to inflammation. As yet no experimental procedure has resulted in the production of lesions that completely resemble those of human Paget's disease. Furthermore, no therapeutic measures are known by which the disease can be controlled or alleviated. While clinicians have employed various measures, none has stood the test of time.

One gross anatomic feature is prominent, and that is that the disease may apparently be limited for some time to a part of a single bone, to an entire bone or to a few bones (especially sacrum and lumbar vertebrae), while at other times many bones may be implicated simultaneously or successively. One must therefore recognize the classic polyostotic clinical form and the subclinical or nonclinical cryptic form that only comes to light at autopsy.

Further, one may surmise that the involvement of numerous bones in Paget's disease does not necessarily indicate that the condition is a generalized disease in the same sense as one understands the generalized bone involvement of osteitis fibrosa cystica or osteoporosis. The disease picture in the latter conditions is brought about by systemic factors affecting the entire skeleton at the same time. As a result, lesions are produced which are generalized, although they are more prominent at certain sites of greater susceptibility.[55] As opposed to such pathogenesis, Paget's disease is to be considered as a condition arising locally, albeit a metabolic factor cannot be excluded as a provocative element.

What produces the local disturbance that eventuates in the disease picture and what part is played by the marrow have not as yet been fully elucidated. Looser,[56] following the view held by Paget, believes that the marrow and bone changes are the result of chronic irritative or of an inflammatory process, first affecting the marrow. On the other hand, it seems more likely that the appearance of fibrous tissue in the marrow is a secondary response, though it undoubtedly has great

55. Jaffe, H. L.; Bodansky, A., and Blair, J. E.: Arch. Path. **12**:715, 1931.
56. Looser, E.: Schweiz. med. Wchnschr. **7**:598, 1926.

importance. Paget's disease is therefore conceived as starting with resorption of the bony substance, followed shortly thereafter by marrow changes, this view being strongly supported by Schmorl. The proliferation of the osteogenic marrow connective tissue is probably more than a reactive phenomenon, for this tissue possesses, in some cases, considerable potentialities of growth. The capacity of the osteogenic marrow connective tissue to undergo unrestrained growth, leading in some instances of the polyostotic form to malignant tumor, stamps the reactive process of Paget's disease as being distinct from that of all the other dystrophic bone diseases. Any evaluation of the connective tissue reaction must consider this feature of the disease.

What induces the initial resorption is not known, but it may well be that the cause of the initial resorption is related to the conditions that ordinarily set up the changes of senile bone atrophy. This impression is sustained by the fact that systematic examination in this disease sometimes discloses simple smooth atrophy of one of the bones, while other bones are thickened and show the typical pathologic changes. It may possibly be that the initiating cause of Paget's disease is a breakdown of the normal mechanism of creeping replacement to which bone is constantly subject. The smooth resorption that results may progress to senile bone atrophy in some persons, while in others in whom reactive and compensating responses appear the osteogenic marrow connective tissue proliferates. This attempts to form new bone by the process of connective tissue bone formation. Transformation of the connective tissue bone into lamellar bone is frequently abortive, and is followed by partial resorption. This stimulates the reparative process further. A vicious cycle of bone formation and resorption is thus set up, and because neither of these mechanisms can go their normal course, the chaotic architecture described under "Microscopic Anatomy" results. Only when a balance is struck between resorption and deposition does a tendency to more normal bone formation or healing appear.

Notes and News

Scientific Exhibit at Milwaukee.—Attention is drawn to the fact that February 13 is the final date for filing applications for space in the Scientific Exhibit at the Milwaukee Session of the American Medical Association, June 12 to 16, 1933. Application blanks may be obtained from the Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago.

University News, Promotions, Resignations, Appointments.—The Charles Mickle fellowship of the University of Toronto has been awarded to Gaston Ramon, director of the farm of the Pasteur Institute in Paris, in recognition of his work on protection against diphtheria.

E. R. Hitchner has been appointed head of the department of bacteriology of the University of Maine, succeeding F. L. Russell, retired.

Aldo Castellani has been appointed director of the Ross Institute for Tropical Diseases in London, succeeding the late Ronald Ross.

The Paul Ehrlich Foundation in Germany has awarded its gold medal to Oswald T. Avery of the Hospital of the Rockefeller Institute for Medical Research, New York, and its silver medal to Michael Heidelberger, associate professor of biochemistry in the College of Physicians and Surgeons, Columbia University, for their chemo-immunologic discoveries.

Cancer Research Institute, Copenhagen.—It is reported that a cancer research institute has been established in Copenhagen through the cooperation of the Danish government, the new Carlsberg Foundation and the Rockefeller Foundation. The institute will be under the direction of Albert Fischer, previously associated with the Kaiser Wilhelm Institute in Berlin.

Béla Schick Awarded Phi Lambda Kappa Medal.—The annual gold medal of the Phi Lambda Kappa Fraternity has been awarded the Béla Schick, Mount Sinai Hospital, New York, for his discovery of the Schick test for diphtheria.

International Congress of Microbiology Postponed.—The International Congress of Microbiology, which was to have been held in Berlin in 1933, has been postponed to 1934.

Association of American Physicians.—The forty-eighth meeting of the Association of American Physicians will be held in Washington, D. C., on May 8 and 10, 1933, in conjunction with the Congress of Physicians and Surgeons.

Obituary

WILLIAM B. BREBNER
1903-1932

In the course of his experiments on infantile paralysis, Dr. Brebner was bitten by a monkey and died of respiratory paralysis ten days later (November 9). He was working at the time in the Bureau of Laboratories of the city of New York as assistant professor of bacteriology in New York University. The particular monkey was not being subjected to any experimental procedure and was merely being removed from a sack in which it was transferred from the animal room to the laboratory. Dr. Brebner's scientific career was short. He graduated in medicine from the University of Toronto in 1926, spent two years working with Dr. Banting and then came to Washington University, St. Louis, where he devoted his entire attention to the problem of infantile paralysis, working under a grant from the International Committee for the Study of Infantile Paralysis (financed by Mr. Jeremiah Milbank) until he accepted the appointment in New York as assistant professor under Dr. William H. Park in February, 1932. But he made the best possible use of the time at his disposal. While still in Toronto, he contributed to our knowledge of tumors, and in St. Louis he was successful in purifying the virus of infantile paralysis to a degree never before secured. His paper on the subject, written in cooperation with Morris Schaeffer, will soon be published in the ARCHIVES OF PATHOLOGY. Dr. Brebner played an active part in combating the 1931 New York epidemic, and was deeply interested in the study of a number of research problems on filtrable viruses at the time of his death. His personality was an attractive one; all his associates were devoted to him and felt that he had a bright future before him. During the past summer he made the first convincing demonstration on a large scale at Bradford, Pennsylvania, of the value of the injection of parents' blood in affording temporary protection against infantile paralysis. The results were published by Williams and Wilkins in October as an addendum to a volume on "Infantile Paralysis" prepared by the aforementioned International Committee. Dr. Brebner lived only long enough to learn that for the present the 1,300 children so treated were safe despite many cases of the disease in others in the same town.

E. V. COWDRY, M.D.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

PATHOLOGIC PHYSIOLOGY OF INFLAMMATION. FISCHER-WASELS, Frankfurt. Ztschr. f. Path. **42**:1, 1931.

This subject is discussed in a series of five articles written by the author and four assistants. The articles are not adaptable to abstract, and the original communication should be consulted.

O. SAPHIR.

THE FATE OF SURFACE EPITHELIUM TRANSPLANTED INTO THE DEEPER TISSUES AND THE RELATION OF SUCH EPITHELIUM TO EPITHELIAL CYSTS. J. L. ZIMCHES, Frankfurt. Ztschr. f. Path. **42**:203, 1931.

Epithelial structures with the adjacent connective tissue were transplanted into various regions of deeper tissues of the same animal in a series of experiments on 102 dogs. The author summarizes his results as follows: A portion of the transplanted skin or mucous membrane heals with the formation of granulation tissue. Implanted surface epithelium forms cysts. The content of the cysts depends on the character of the transplanted epithelium. In the case of transplanted ureteral mucosa, the content of the cysts is an albuminous liquid. When skin is transplanted the content of the cyst consists of keratinized epithelium and hairs. The tendency of transplanted surface epithelium to form cystic cavities follows a law that governs the growth of epithelium in general, namely, that the more active growth always is directed toward the nearest island or margin of epithelium. Traumatic epithelial cysts of the finger or hand take their origin from epithelial cells which, by trauma, have been implanted in the deeper layers. Implanted surface epithelium does not undergo metaplastic changes. However, a heteroplastic metaplasia of connective tissue into bone structures was observed in some instances when ureteral tissue was transplanted.

O. SAPHIR.

DIABETES INSIPIDUS IN A PATIENT WITH TUMOR METASTASIS TO THE HYPOPHYSIS. W. GRASMANN, Frankfurt. Ztschr. f. Path. **42**:384, 1932.

Fifteen years before death, a woman 54 years old was operated on for carcinoma of the breast. Two months prior to death psychic changes were noted. Later she complained of great thirst. There was, however, no sugar in the urine. During her stay at the hospital she also complained of severe headache. The daily urinary output varied between 2,300 and 3,500 cc., with a specific gravity of from 1.001 to 1.005. No chemical changes were found in the urine. At autopsy there were a recurrent carcinoma of the axillary region and metastases to the pleurae, liver, thyroid gland, left suprarenal gland, midbrain and hypophysis. The posterior lobe of the hypophysis was infiltrated with carcinomatous structures, while the anterior lobe in general showed no changes. Also, the hypophyseal duct was partially replaced by the tumor. Because the midbrain was also involved, the author could not decide whether the diabetes insipidus was caused by the tumor in the hypophysis or by that in the midbrain or by both.

O. SAPHIR.

VITAMIN E DEFICIENCY. A. JOHÁSZ-SCHÄFFER, Virchows Arch. f. path. Anat. **281**:3, 35, 46, and 53, 1931.

In four consecutive articles, the author presents the results of an experimental study of the effects on rats of a deficiency of vitamin E. Both male and female rats maintained on a synthetic diet devoid of this vitamin were incapable of

reproduction. In the males, the loss of fecundity was associated with severe changes in the testes. The germinal epithelium of the seminal tubules underwent degeneration and necrosis, spermatogenesis ceased, and in the terminal stages the tubules contained only a single layer of cells. The Sertoli cells and the interstitial tissue revealed no changes. In females, in spite of the loss of fecundity, no morphologic alterations in any of the structural elements of the ovary could be detected. The addition of vitamin E (wheat germ oil) to tissue cultures caused active proliferation of the cells, and the zone of active growth was greater than in control cultures. Inactivated oil did not have a similar stimulating effect. Both the active and the inactivated oil were taken up in equal degree by the culture cells, leading to the conclusion that the growth-promoting action is due to the vitamin and not to the nutritive properties of the substance used. Rats could not be accustomed to the deficiency by gradual withdrawal of the vitamin-containing substance. When an excess of vitamin E was fed and the material was then suddenly withdrawn, evidences of deficiency manifested themselves. When an excess of vitamin E was fed, it was excreted in the feces in quantities sufficient to render the feces protective against avitaminosis in rats for which such feces were the only available source of vitamin. The feces of rats on the deficient diet had no such protective action, leading to the conclusion that vitamin E is not formed in the intestinal canal as the result of bacterial action.

O. T. SCHULTZ.

COMBINED DISEASE OF THE SUPRARENAL AND THYROID GLANDS. RUTH KÖHLER, Virchows Arch. f. path. Anat. **281**:466, 1931.

The increasing number of reports of cases of Addison's disease due to atrophy of the suprarenal cortex includes those of cases that reveal also changes in the thyroid gland. In some of the cases of combined disease, to which M. B. Schmidt has devoted special attention, no symptoms of a dysfunction of the thyroid gland have been evident, either because they were masked by the symptoms of Addison's syndrome or because the degree of involvement of the thyroid gland was not great enough to have caused manifestations. Some have exhibited the symptoms of hyperthyroidism; others, of hypothyroidism. The author presents two cases of Addison's disease due to atrophy of the suprarenal cortex. In one, similar atrophic changes were present in the thyroid gland; in the other, such alterations were not evident. Contrary to the opinion expressed by some, that the involvement of the thyroid gland is secondary and due to the atrophy of the suprarenal cortex, the author believes that atrophy of the thyroid gland and lymphocytic infiltration, when associated with atrophy of the suprarenal cortex and clinical Addison's disease, are independent of the changes in the suprarenal cortex and are the result of a constitutional factor that involves the two elements of the endocrine system.

O. T. SCHULTZ.

EFFECT OF PARTIAL RESECTION ON THE THYROID GLAND. W. HARTOCH, Virchows Arch. f. path. Anat. **281**:507, 1931.

In each of twelve dogs, a lobe or a part of a lobe of the thyroid gland was resected. From fourteen to twenty days later the rest of the gland was removed. The tissues removed at the two operations were subjected to comparative histologic study. The height of the epithelium and the diameter of the follicles were measured and average figures obtained. The character of the colloid was determined by its staining reactions. The height of the epithelium and the average diameter of the follicles remained unaltered. In the control tissues, or the first resected, differences in the consistency of the colloid were evident, dependent on the age, sex and general condition of the animals. Resection led to no consistent changes in the character of the colloid. In some animals, it remained unchanged; in others, the relative amount of thick colloid was increased; in still others, the colloid became thinner. The author interprets his findings to mean that morphologic alterations in the thyroid gland are not adequate criteria for determining the action of iodine or other factors on this gland.

O. T. SCHULTZ.

QUANTITATIVE DISTRIBUTION OF THE BLOOD. A. HINTZE, Virchows Arch. f. path. Anat. **281**:526, 1931.

This study of 175 pages from Bier's surgical service at the University of Berlin seeks to evaluate some of the factors that control the distribution of the blood in the absence of regulation by the central nervous system. The experimental procedure employed was the perfusion of animals with intact circulation, killed at the moment of perfusion, and the perfusion of amputated human limbs and of new-born infants who had died during the course of delivery or shortly thereafter. The perfusing material was 5 per cent acacia solution, colored by the addition of dye or other substance. The duration of the perfusion and the quantity of gum arabic solution used were such as would cause complete filling of the circulatory system at a pressure equal to the arterial pressure of the experimental object. The quantitative distribution of the perfused material was estimated by the depth of color exhibited by the various tissues, organs and parts of the body. In animals, the hypophysis, the thyroid gland and the suprarenal glands received relatively the largest quantity; the brain and spinal cord the next largest, and the gonads, the bones of the extremities and the adipose tissue relatively the least. The quantity delivered to an organ could not be estimated from the diameter of the artery supplying it, but depended on the resistance offered by the vascular bed of the organ. This resistance depended on the anatomic structure of the vascular bed and on the tonus of the small arteries and capillaries. Warmth and epinephrine increased the rate and quantity of distribution. Epinephrine added to the solution of gum arabic reached the brain more quickly than it did other parts of the body. The respiring lung received a larger quantity of liquid than the quiescent lung; a loop of intestine filled with milk, more than adjacent collapsed loops. In amputated human limbs and in new-born infants, the findings were in general similar to those obtained in animals. Tonus that had disappeared could be restored by warmth, epinephrine or chemical stimuli. Alterations in distribution associated with functional states, such as active or nutritional hyperemia, could not be elicited in the surviving organism. External hydrostatic pressure caused slight narrowing of the dilated vessels. External heat within physiologic limits resulted in increased flow; cold, in decreased flow. Increasing the temperature of the solution used to 45 C. and decreasing it to 11.5 C. caused, respectively, dilatation and contraction of the small peripheral vessels and the opposite effect on the larger vessels. Vessels the spontaneous contraction of which had emptied the tissues of blood did not react to temperature, but required a chemical stimulus to bring about an increase in caliber. Epinephrine and pituitrin increased the distribution to the head, extremities and muscles, and decreased it to the abdominal organs. Epinephrine acted more strongly than pituitrin. The vessels retained their reactivity for as long as three weeks if the tissues were kept in the cold. Reaction to mechanical stimuli was lost first, and that to temperature next. Contraction of the small vessels by epinephrine could be elicited even after considerable postmortem change had occurred in the tissues.

O. T. SCHULTZ.

PATHOLOGIC ANATOMY AND ABNORMAL PHYSIOLOGY OF THE SUPRARENAL GLANDS. F. PAUL, Virchows Arch. f. path. Anat. **282**:256, 1931.

In a monograph of 146 pages, Paul attempts to correlate the pathologic anatomy of the suprarenal glands with the abnormal physiologic manifestations during life. He presents first, as examples of chronic and acute hyperfunction of the suprarenal medulla, cases of chromaffin tumors of these glands. In two chronic cases, the clinical manifestations were those of chronic nephritis, with hypertension, albuminuria, albuminuric retinitis and uremia, without renal changes sufficient to account for these symptoms. In the acute cases, the symptoms were those of acute intoxication with hypertension and low blood sugar. The tumor in each case was composed of cells that gave a strong chromaffin reaction. Paul ascribes the nephritic and toxic symptoms in the chronic and acute cases to hyperadrenalemia. He expresses the view than many of the symptoms of essential hypertension and chronic

nephritis are the result of the action of toxins and other endogenous and exogenous factors on the suprarenal glands, leading to hyperfunction of the medulla and to increased output of epinephrine. As an example of hyperfunction of the suprarenal cortex, he presents a case of virilism in a woman aged 35, who had a hypernephroma (cortical carcinoma) of the left suprarenal gland. He discusses critically the views of the origin and nature of hypernephroma of the kidney, for no instance of which, according to him, has there ever been described a hormonal action on the genital sphere comparable to that of hyperplastic tumors of the suprarenal cortex, and he concludes that renal hypernephromas are nephrogenic and are not derived from misplaced suprarenal cortical tissue. Two cases of Addison's disease with so-called cytotoxic atrophy of the suprarenal cortex are presented as examples of suprarenal hypofunction. They furnish the basis of a full discussion of the relation of atrophic changes limited to the cortex to clinical Addison's disease. Paul disagrees with Kovacs and others, who sought to establish the identity of an incomplete Addison's syndrome with normal blood pressure due to loss of cortical activity alone. To determine the effect of toxic factors on these glands, Paul made a histologic study of them in 33 cases of acute infection, 71 of subacute and chronic infection, and 54 of chronic intoxication. Round cell infiltration was noted in 51, 80 and 60 per cent, respectively, of these three groups. Areas of fat cells were noted in 3, 42 and 15 per cent, respectively. The results of the examination of the 158 cases are presented in tabular form. Paul claims that both the medulla and the cortex are injured by toxic agents, that the cortex is not injured specifically and alone, and that Addison's disease is the result of hypofunction of the entire organ.

O. T. SCHULTZ.

RESPIRATORY METABOLISM AND TISSUE RESPIRATION IN EXPERIMENTAL ANAEROBIC INFECTION. G. SCHMID, Virchows Arch. f. path. Anat. **282**:540, 1931.

Research on anaerobic bacteria and on the infections caused by them being, according to the author, in a state of stagnation, he undertook an experimental investigation along new lines, the results of which are here reported. One set of experiments consisted in the determination of the oxygen consumption, carbon dioxide production and respiratory quotient of guinea-pigs infected with the organism of malignant edema, the results obtained being compared with those for the same animals before infection. Similar determinations were made on a small series of animals infected with the aerobic organism of fowl cholera. The figures are so variable and inconstant as not to warrant any conclusions. Tissue respiration was studied by the method of decolorization of methylene blue (methylthionine chloride, U. S. P.) solution. The muscle of animals infected with malignant edema decolorized the solution more slowly than the muscle of animals infected with fowl cholera. It is to be said in the author's favor that he himself does not draw any unwarranted conclusions from what must have been time-consuming work, but he does present, as a set of conclusions to his forty-five page article, three pages of suggested further research.

O. T. SCHULTZ.

EFFECT OF DEFICIENCY OF VITAMIN E ON THE FEMALE RAT. A. JUHÁSZ-SCHÄFFER, Virchows Arch. f. path. Anat. **282**:662, 1931.

In a previous series of communications, which have been abstracted in the ARCHIVES, the author showed that a deficiency of vitamin E in the diet of male rats resulted in sterility through the complete inhibition of spermatogenesis. In female rats on a similar diet, no histologic abnormalities of the ovary could be detected, follicular development and ovulation proceeding in normal manner. Such females became impregnated, but failed to give birth to young. In the present experiments, females maintained on a diet deficient in vitamin E were mated with males kept on an adequate diet. The fecundity of the males was established by their ability to impregnate normal females. Females that became impregnated

shortly after being placed on the deficient diet gave birth to young, most of which were dead; the few living young died within a few days after birth. The next pregnancy of such females resulted in a smaller litter of young, all of which were born dead. In succeeding pregnancies, the number of young, all born dead, decreased, until finally no young were born, all having died in utero and undergone resorption. If the female was now placed on a diet containing vitamin E, successive pregnancies resulted in the birth of young, the number of living young being inversely proportional to the number of pregnancies without delivery through which the female had passed. Deficiency of vitamin E does not cause sterility in the female, but only an inability to bring forth living young. The deficiency acts apparently, not on the female, but on the young. Work previously abstracted showed that the addition of wheat germ oil containing vitamin E to cultures of rat tissues brought about an increased rate of growth of the tissue. In explanation of the so-called sterility of the female, the author postulates that the deficiency of vitamin E inhibits the rapid cellular divisions of the early stages of the embryos, just as it inhibits the rapid cellular divisions necessary for spermatogenesis.

O. T. SCHULTZ.

POTENTIALITIES OF CAPILLARY ENDOTHELIUM. E. KUX, Virchows Arch. f. path. Anat. **282**:844, 1931.

This is a contribution to the controversy over the vital storage activities and potencies of the capillary endothelium of the general vascular system. India ink, carmine and trypan blue were injected intravenously into frogs and the results studied in the living tongue and in fixed preparations. When india ink was injected, the pigment granules were quickly taken up by the capillary endothelium. From these it was passed on to the pericytes and tissue histiocytes and was deposited in the connective tissue surrounding the vessels. The material was also taken up by the white cells of the circulating blood, chiefly by the lymphocytes and monocytes, and to a lesser degree by the granulocytes and thrombocytes. These cells left the circulation and also deposited their carbon granules in the connective tissue. The blood was quickly cleared of the foreign particles, but the latter were held for long periods in the connective tissue. No freeing of endothelial cells into the lumen of the vessels, with a theoretically possible transformation into blood cells, was noted, and no transformation of endothelial cells into wandering cells that migrated into the surrounding tissues was seen. Carmine and trypan blue were taken up by the blood and tissue histiocytes, but not at all, or only in the slightest degree, by the capillary endothelium. The author concludes, in agreement with Maximow and others, that the capillary endothelial cell of the general vascular system is a cell of highly differentiated type, and that, although it can phagocytose relatively coarser particles, like those of india ink, it is not capable of transformation into a blood cell, a histiocyte, a fat cell or a cell of other type.

O. T. SCHULTZ.

THE FUNCTION OF THE TONSILS. H. SCHERF, Virchows Arch. f. path. Anat. **283**:74, 1932.

Full-grown rabbits were used in an investigation of the function of the tonsils. When colloidal trypan blue or silver or finely particulate india ink was painted on the surface of the tonsils, the material was not taken up by the lymphoid tissue. Spraying of the same substances into the pharynx led to deposition of the material on the surface epithelium, but it was not transferred to the tonsil itself. The surface of the tonsil may mechanically remove foreign particulate matter from inspired air. When the experimental materials were injected into the submucous tissues of the nasopharynx and mouth, they were stored in macrophages of the peritonsillar tissue, but did not reach the tonsillar tissue itself, indicating that peritonsillar inflammatory processes may result from lymphatic transport from the submucous tissues. When the materials were injected into the

common carotid artery, the material was stored in the capillary endothelium, from which it was passed to the surrounding tissue. This process was most marked in the subepithelial capillaries, the material passing to the surface of the tonsil and being excreted. The tonsils may apparently function in the removal of foreign material from the blood stream.

O. T. SCHULTZ.

EXPERIMENTAL TRANSMISSION OF HARMFUL EFFECTS OF VIOSTEROL FROM MOTHER TO YOUNG. AGATHE JUNCK, Virchows Arch. f. path. Anat. **283**:265, 1932.

Accidental discovery of the arterial lesions of D-hypervitaminosis in two young of a rabbit that had received viosterol before pregnancy led to investigation of the transmission of the harmful effects of the vitamin. It was found that adult female rabbits in which severe arterial disease had been produced by viosterol, administered either in large doses over a short period of time or in small doses over a longer period, regularly gave birth to young in which arterial lesions developed at an age much earlier than that at which vascular damage occurs spontaneously in rabbits. Such young received no viosterol. That the damage was not due to an excess of vitamin in the milk of the mother was established by the fact that the young born while the mother was receiving the vitamin or shortly after the administration was stopped, but before severe arterial disease had developed in the mother, remained normal, whereas the young of later litters, the mother having received no additional viosterol in the meantime, showed lesions. The author believes that the damage to the young is the result of intra-uterine injury of the young by a metabolic disturbance of the mother, which manifests itself in her own arterial disease, and which persists after cessation of the administration of the vitamin.

O. T. SCHULTZ.

Pathologic Anatomy

CARDIAC RUPTURE WITH PERFORATION OF INTERVENTRICULAR SEPTUM. WALTER FREEMAN and EDGAR DEUCHER GRIFFIN, Am. Heart J. **7**:732, 1932.

Two cases of perforation of the interventricular septum following coronary thrombosis are reported. This rare condition should be suspected when there is superimposed on the picture of coronary occlusion a striking symptom complex consisting of (*a*) progressive harsh systolic murmur and thrill over the precordium, (*b*) gradual extinction of the aortic second sound and (*c*) marked disproportion between the force of cardiac action and the strength of the pulse. The mechanism seems plainly indicated. The septal perforation permits passage of blood from the stronger left ventricle to the weaker right through a gap with rough edges reducing the stream that passes the normal aortic opening into the general circulation. Death may take place from pulmonary congestion and edema before the opening is large enough to divert sufficient blood from the systemic circulation to cause disappearance of the pulse. The condition may be distinguished from congenital malformation by the age and previous condition of the patient as well as by the shorter survival period.

AUTHORS' SUMMARY.

ANEURYSM OF THE AORTA PRODUCING PULMONARY STENOSIS AND BUNDLE-BRANCH BLOCK. J. HAMILTON CRAWFORD and J. ARNOLD DEVEER, Am. Heart J. **7**:780, 1932.

A case of syphilitic aortitis is reported in which an aneurysm 9 cm. in diameter, arising in the first portion of the ascending aorta, had produced none of the usual clinical evidences of aortic aneurysm. A high grade bundle-branch block was known to have been present for a period of eleven months prior to death from myocardial failure. The aneurysm, which had not ruptured, caused marked stenosis of the pulmonary artery and insufficiency of the pulmonary valve. It projected into

the right ventricle and produced considerable damage to the interventricular septum. This appeared to be the most important factor in the causation of the bundle-branch block. Slight aortic insufficiency was also present.

AUTHORS' SUMMARY.

CAUSES OF DEATH IN STILLBIRTHS. J. B. GILLESPIE, Am. J. Dis. Child. **44**:9, 1932.

In 388 postmortem examinations of stillborn infants from a rather extensive metropolitan area, the cause of death in 30 per cent of the cases was trauma at birth, and in 16 per cent it was prematurity, while 20 per cent of the cases constituted a group of macerated and fresh fetuses in which the cause of death was not determined.

RALPH FULLER.

MASSIVE INTRA-ABDOMINAL HEMORRHAGE IN THE NEW-BORN. S. NUSSBAUM, Am. J. Dis. Child. **44**:146, 1932.

Two cases of massive intra-abdominal hemorrhage in the new-born are described. In one case, the hemorrhage originated in the liver, where trauma due to forceful methods of resuscitation produced two subcapsular hemorrhages into the liver tissue. In the other case, the hemorrhage came from the right suprarenal gland, where a large intrasuprarenal hemorrhage preceded the abdominal hemorrhage. Both patients died on the fourth day of life, when the greatest incidence of hemorrhagic disease of the new-born occurs. This was considered an important factor.

AUTHOR'S SUMMARY.

SPONTANEOUS GANGRENE OF THE EXTREMITIES. L. D. SMITH, Am. J. Dis. Child. **44**:151, 1932.

Fulminating, destructive symmetrical gangrene occurred in an epileptic girl, 7 years of age, with an acute respiratory infection, after she was suddenly exposed, incompletely clothed, to zero temperature. Any one of these conditions might be expected to conduce to neurovascular changes. That there was a temporary increase in coagulability of the blood of both legs in association with the respiratory infection may be presumed. The final result was thrombosis of the arteries and veins with inflammatory infiltration around the vessels.

AUTHOR'S SUMMARY.

ERYTHROBLASTIC ANEMIA. LEWIS A. KOCH and BENJAMIN SHAPIRO, Am. J. Dis. Child. **44**:318, 1932.

Erythroblastic anemia should be considered as a definite disease entity. It is otherwise variously known as racial or familial hemolytic anemia and has recently been separated from the heterogeneous group of so-called von Jaksch's or splenic anemia. The onset is in early infancy and is accompanied by splenomegaly and some degree of icteric discoloration of the skin. There may be progressive enlargement of the cranial and malar bones with an associated mongoloid facies. The blood frequently reveals besides the low hemoglobin and the erythroblastosis, a leukocytosis of varying degree and often an increase of myeloid or lymphoid cells. There is evidence of increased hemolysis in the high icterus index and positive van den Bergh reactions, although the fragility of the red cells is not increased. Eighteen cases that have shown the changes in the bones are summarized from the literature, and five additional cases, one with necropsy, are reported. Necropsy was made on a girl of 18 months, who was observed throughout her entire illness, and in the beginning there was little to indicate the future course other than the grave anemia. However, after observing the progress and later enlargement of the cranial bosses with no demonstrable evidence of rickets, the type of anemia described by Cooley was considered. Roentgenograms of the skull and bones became more characteristic until finally the case was typical. At necropsy the spleen and liver were found grossly enlarged. Microscopic sections of the liver,

pancreas, thymus, lymph nodes and periosteum gave strong positive reactions for iron. The splenic pulp was moderately fibrotic and possessed numerous wide sinusoids; myeloid and lymphoid cells were found in about equal proportions. The enlarged lymph nodes contained many myeloid cells and dense subcapsular collections of large phagocytic cells laden with hemosiderin. The calvarium was unusually thick, particularly in the frontal and parietal regions; the bone was soft and purplish red on section, lacking the usual division into inner and outer tables with diploe between them. The long bones were normal in shape but possessed unusually thin cortices. The bone marrow was very cellular with uniform distortion of the bony trabeculae and lack of cortical condensation. Leukoblastic cells were seen to comprise almost the entire marrow, but there were subperiosteal collections of large hemosiderin-laden phagocytic cells. RALPH FULLER.

RACIAL OR FAMILIAL ANEMIA OF CHILDREN. G. H. WHIPPLE and W. L. BRADFORD, Am. J. Dis. Child. **44**:336, 1932.

Three cases are reported of a condition which evidently belongs in the group described by Cooley as erythroblastic anemia. Two patients were siblings, and all were of Italian parentage. Necropsy was made on the body of a girl 5 years of age. There was pigmentation of the viscera and lymph nodes. The pancreas possessed a buff color suggesting that of the pancreas in hemochromatosis. The liver and spleen were enlarged. The thymus was small and not grossly pigmented. The calvarium was greatly thickened, and on section the tables were widely separated and largely obliterated, the greater part of the bone being made up of chocolate-red, spongelike marrow in which there were rather heavy bone trabeculae. The ribs were greatly thickened and spongy on section. The cortex of the femur was reduced almost to egg-shell thickness, and the hyperplastic chocolate-brown marrow contained large bony spicules. Microscopically there was considerable splenic fibrosis, and the sinusoids were conspicuous; in some areas there were numbers of foam cells, and eosinophilic cells were fairly numerous and widely scattered. Bone marrow obtained from various regions presented similar microscopic pictures; nucleated red cells and large parent cells of undefined type were numerous, and there were many clustered myelocytes and nests of foam cells occasionally containing blood pigment. Tissue sections treated to demonstrate iron showed positive granular deposits in scattered lymph nodes and mucous and serous glands, in the acinar epithelium of the pancreas, in the liver cells of the peripheral half of the lobule, in the gastric secretory epithelium, especially in the chief cells, in the acinar cells of the thyroid, in the entire parathyroid parenchyma, in the reticulum of the thymus, in the foam cells and phagocytes of the bone marrow and in the acinar cells of the pars anterior of the hypophysis.

RALPH FULLER.

AGLOSSIA CONGENITA. ROBERT ROSENTHAL, Am. J. Dis. Child. **44**:383, 1932.

In the case reported, there was almost complete absence of the tongue; the notched bud in front apparently represented a rudiment of the lateral tongue swellings. There was no evidence of the part normally formed from the tuberculum impar or of the radix linguae. The nondevelopment of the anterior part of the tongue and the underdevelopment of the mandible occur together, as both originate from the same visceral arch. In cases of agnathia the tongue, at least the anterior part, is always absent. The lower parts of the tonsils help to form a part of the posterior floor of the mouth. The absence of the lower incisors and the consecutive narrowing of the floor space make it easier for the left hypertrophic sublingual ridge to form part of the floor of the mouth and to aid in the act of mastication, especially as this ridge seems to contain muscle fibers, which make some voluntary motions possible. Teratologically, one has to assume that in the case reported the damage must have occurred at a very early age in order to produce anomalies in so many and in such widely separated organs.

AUTHOR'S SUMMARY.

HEREDITARY ECTODERMAL DYSPLASIA, ANHIDROTIC TYPE. MENDEL ZELIGS, Am. J. Dis. Child. **44**:394, 1932.

The characteristics are congenital absence of the sweat glands and absence of the pilosebaceous apparatus over most of the body, with resulting intolerance for heat. There are marked dental aplasia, a depressed nasal bridge, atrophic rhinitis, prominent supra-orbital ridges and thick, protruding lips. The skin is very white, thin, dry, smooth and soft, and shows the superficial veins plainly. This case differs from the others of this type reported in that, although there is absence of sweat and sebaceous glands, the hair follicles are normal in appearance and fairly numerous. The only other characteristic observation was the absence of teeth with the exception of the two peg-shaped upper central incisors. The bridge of the nose was normal, but there was a mild rhinitis. The supra-orbital ridges and the lips were not abnormal. As the child was only 10 months old, it is quite possible that atrophic rhinitis with resulting depression of the nasal bridge might have developed later. Unfortunately, only skin from the abdomen was examined microscopically, but the entire block was sectioned serially and carefully studied, and no sweat or sebaceous glands were found.

AUTHOR'S SUMMARY.

ARTERIOLAR STUDIES IN PATIENTS WITH HYPERTENSIVE HEART DISEASE WITHOUT HYPERTENSION. EMMET F. HORINE, MORRIS M. WEISS and MARION F. BEARD, Am. J. M. Sc. **184**:206, 1932.

Biopsy specimens of the deltoid muscle were obtained from eleven patients with cardiac enlargement but normal blood pressure and no other factor to explain the enlargement. Histologic changes in the intima and media of the arterioles similar to those encountered in known hypertensive patients were found in all. Careful measurements of the arterioles of the specimens gave a ratio of the wall to the lumen of from 1 to 1.31 to 1 to 0.7, similar to ratios found in known hypertensive patients and in marked contrast to the normal ratio of 1 to 2. Three patients are now dead, and one autopsy specimen was obtained in which a generalized arteriolar sclerosis was found. The frequency with which persons with hypertension show arteriolar lesions of the voluntary muscles is discussed. A diagnosis of "hypertensive heart disease without hypertension" may be confirmed by biopsy of the voluntary muscles.

AUTHORS' SUMMARY.

STUDIES IN ATHEROSCLEROSIS. PEARL ZEEK, Am. J. M. Sc. **184**:350 and 356, 1932.

A review of 1,070 consecutive autopsies performed on persons under 30 years of age revealed atherosclerosis occurring with far greater frequency in connection with certain diseases than with others. Rheumatic heart disease was almost invariably accompanied by atheromatous changes in the aorta, pulmonary or coronary arteries. All of the 4 diabetic patients presented atherosclerosis of the aorta. Chronic renal lesions were found in 34 of the 52 nondiabetic, nonrheumatic patients who presented atherosclerosis, and were present also in 10 of the 23 rheumatic patients. The renal arterioles were the vessels most frequently involved in these cases. The only other pathologic lesions which occurred with notable frequency in the atherosclerotic group were: (1) focal lesions in the suprarenal medullae and (2) hypoplasia of the malpighian corpuscles in the spleen.

Sixty-two cases of rheumatic heart disease have been analyzed with reference to the incidence of atheroma, particularly in the aorta and coronary and pulmonary arteries. In 28 patients under 31 years of age the degree of atheroma has been compared with the duration and extent of the cardiac lesions. Rheumatic heart disease has been found to predispose to the early development of atheromatous lesions in the aorta and pulmonary and coronary arteries, and also in the valvular and left atrial endocardium. Lipoid deposits also have been found, in some cases, in the inflamed serous membranes and in certain renal tubules. Lipoid deposition has seemed to begin soon after the onset of cardiac disease, and, in a very general

way, has paralleled in degree the cardiac lesions. The atheromatous changes, in many cases, have been progressive, leading to calcification and, when in the valvular endocardium, accentuated stenosis.

AUTHOR'S SUMMARY.

MYOCARDIAL INFARCTION OR GROSS FIBROSIS. JAMES R. LISA and ALFRED RING, Arch. Int. Med. **50**:131, 1932.

Recent cardiac infarction and coarse myocardial fibrosis interpreted as healed infarction are extremely common observations at autopsy. They are usually associated with coronary sclerosis and cardiac hypertrophy. Males are more frequently affected than females; the proportion is 5:1. The average age is approximately 60 years, but there is a very wide variation. Hypertension is present in approximately 60 per cent of the cases. Only slightly more than one half of the patients presented clinical features of cardiac disease. Changes in the T wave and Q-R-S complex are the most frequent electrocardiographic abnormalities. Patients presenting anginal or dyspneic syndromes are more prone to death from acute cardiac infarction than those with the congestive or combined type. Of the noncardiac cases, approximately 20 per cent terminate with recent cardiac infarction. In approximately one half of the latter cardiac symptoms develop as a terminal event. In the large majority of cases with coarse fibrosis interpreted as healed infarction there is no history of a previous cardiac accident.

AUTHORS' SUMMARY.

SMALL FOCI OF DEMYELINIZATION IN DIFFUSE SCLEROSIS. FREDERIC WERTHAM, Arch. Neurol. & Psychiat. **27**:1380, 1932.

Wertham describes two cases of diffuse sclerosis in adults, one of eight and the other of about twelve years' duration. In both cases, one of which gave a clinical picture of multiple sclerosis, extensive foci of demyelinization were found in the hemispheres, basal ganglia and spinal cord. Not only the white, but the gray, substance was involved and the U-fibers in the cortex were occasionally preserved. Wertham considers the process degenerative, not infectious and inflammatory. The small areas of sclerosis much resemble those in dementia paralytica and multiple sclerosis. The differential diagnosis is not possible from the aspect of the patches alone but may be helped by their number and mode of distribution and the type of the concomitant histologic changes. At any rate, the changes are not secondary, even when present in the spinal cord. GEORGE B. HASSIN.

CHRONIC SYPHILITIC POLIOMYELITIS. N. W. WINKELMAN, Arch. Neurol. & Psychiat. **28**:151, 1932.

In the hands and neck of a man, aged 50, with a history of syphilis and a positive Wassermann reaction in both the blood and the spinal fluid, marked muscular atrophy developed; the pupils were frozen, and the colloidal gold curve was of the dementia paralytic type. The anterior horns in the cervical and upper thoracic regions were shrunken, with atrophy of the medullated nerve fibers and of the ganglion cells. The meninges were infiltrated with lymphocytes and a few plasma cells which extended over the anterior and posterior roots. The blood vessel walls showed thickening, hyalinization and adventitial infiltration. Mild changes in the ganglion cells were also present in the medulla, which showed slight perivascular infiltrations. These were also present in the subcortex.

GEORGE B. HASSIN.

NERVE DEGENERATION IN EXPERIMENTAL POLIOMYELITIS. IV. PHYSIOLOGIC AND HISTOLOGIC STUDIES ON THE ROOTS AND NERVES SUPPLYING PARALYZED EXTREMITIES OF MONKEYS DURING ACUTE POLIOMYELITIS. JAMES L. O'LEARY, PETER HEINBECKER and GEORGE H. BISHOP, Arch. Neurol. & Psychiat. **28**:251, 1932.

Certain phases of poliomyelitis in monkeys have been studied by O'Leary and his co-workers by histologic and oscillographic methods for the purpose of deter-

mining the mortality of the cells injured by the virus, the nature of the functional changes in the fibers involved and the rate of disappearance of conductivity in the degenerating fibers of the spinal roots and nerves. The histologic studies in degenerating nerve fibers they correlated with the depression and disappearance of the action potential, by which they determined the site of the functional loss. The peripheral nerves have been removed for histologic and oscillographic studies at various intervals after inoculation. In a monkey killed on the first day of the paralysis, the cell body of the anterior horn was functionally dead, while the peripheral nerves were functionally and histologically normal. After four and one-half days the myelin showed degenerative phenomena, while the axon was still intact; after six days it became varicose. The site of the first functional loss proved to be in the ganglion cell or its synapse with the upper motor neuron, the degeneration proceeding more rapidly in the roots. Yet, regardless of the irresponsiveness of the ganglion cells, many nerve fibers were capable of conducting apparently normal impulses. Any noticeable change in the axons is preceded in poliomyelitis by a motor paralysis. The increase in conduction rate and the shorter refractory period indicate an increase in the irritability of the nerve fibers during the preparalytic stage and the first days of the paralysis. These are only some of the interesting conclusions arrived at from the studies of peripheral nerves and roots from the affected segments of the cord which were contrasted with those from typical normal peripheral nerves.

GEORGE B. HASSIN.

CENTRAL NERVOUS SYSTEM IN ACUTE PHOSPHORUS POISONING. FREDERIC WERTHAM, Arch. Neurol. & Psychiat. **28**:320, 1932.

Wertham examined the brain of a woman, aged 41, who died six hours after she had taken rat poison which contained phosphorus. The ganglion cells of the cortex, especially of the frontal lobe, the inferior olives and the nucleus dentatus, contained an excessive amount of lipoids. The nuclei were darkly stained, and the Golgi nets were incrustated. The basal ganglia were less rich in fat, which was also scarce in the calcarine cortex. The Purkinje cells were fat-free, but the large Golgi cells of the granular layer near the Purkinje cells and the blood vessels in this region exhibit marked accumulation of lipoids. Mesenchymal reaction was absent. In general, lipophilic cells (of Obersteiner) containing much lipofuscin were more infiltrated than the lipobolic (Purkinje cells), which were often spared.

GEORGE B. HASSIN.

CRANIAL HYPEROSTOSIS, ASSOCIATED WITH AN OVERLYING FIBROBLASTOMA. BERNARD J. ALPERS and REED HARROW, Arch. Neurol. & Psychiat. **28**:339, 1932.

The authors report a unique case of cranial hyperostosis secondary to a fibroblastoma, not of the meninges, as is usually the case, but of the bone itself. The tumor originated in a man, aged 23, who at the age of 2 years had sustained an injury to the left side of the forehead. In 1925, the patient sustained another injury in the same location, and a small swelling appeared and grew larger. The main complaints were weakness in the extensor muscles of the left hand, atrophy of the left half of the tongue and deafness, especially in the left ear. A bony tumor, 10 by 7 cm. in the left frontal region was removed, and proved to be a fibroma on the outer table of the skull. It penetrated into the bone along the haversian canals. In some places, large areas of bone were entirely replaced by tumor cells. The dural tissues were normal.

GEORGE B. HASSIN.

SQUAMOUS CELL CARCINOMA OF THE KIDNEY, WITH COMPLETE INFARCTION OF THE KIDNEY, AS A SEQUEL TO CARCINOMATOUS THROMBOSIS OF THE RENAL ARTERY. J. RABINOVITCH, Arch. Surg. **24**:581, 1932.

The carcinoma had invaded and occluded the renal artery, thus causing total infarction of the kidney.

GEORGE B. HASSIN.

CALCIFIED CYSTS OF THE KIDNEY. J. A. C. COLSTON, Bull. Johns Hopkins Hosp. **61**:125, 1932.

A series of six calcified cysts, all proved to be in intimate relation to the kidney, is presented, and in each case an antecedent history of severe injury has been elicited so that there can be little doubt that trauma was the etiologic factor in the causation of these cysts. The perirenal hematoma, of varying extent, which is formed by any injury which tears through the capsule of the kidney into its substance represents the early stage of a calcified cyst. Such a hematoma either may be completely absorbed or, if it is of any extent, it is more probable that the calcium salts which are present in the extravasated blood and urine will be precipitated in the wall. When the cyst has become calcified the wall is found to consist of fibrous tissue with irregular areas of calcification without epithelial lining. In simple serous cysts a definite epithelial lining can often be found so that, if definite traces of epithelium can be found in the wall, it may be assumed that such a cyst has resulted from hemorrhage into a preexistent simple serous cyst.

AUTHOR'S SUMMARY.

MONOCYTIC LEUKEMIA. P. W. CLOUGH, Bull. Johns Hopkins Hosp. **61**:148, 1932.

Cases of leukemia occur in which the predominant cells in the blood and in the tissues are monocytes and their immediate precursors. The occurrence of these cases is a strong argument in favor of the independent status of the monocyte. Previously reported cases have been reviewed, and another case has been reported, together with the hematologic findings and observations at autopsy. Clinically, these cases resemble those of acute leukemia of other types, except for a relatively moderate degree of enlargement of the liver, spleen and lymph nodes. Diagnosis depends on the accurate identification of the predominant cells in the blood. This is based on the morphologic characteristics of the nuclei, cytoplasm and cytoplasmic granules, on the (usually) negative oxydase reaction and particularly on evidences of motility and phagocytic activity. At autopsy the tissues show an extensive leukemic infiltration with monocytic cells, which is analogous to but perhaps more widely distributed than that in other types of leukemia. An interesting appearance of swelling and desquamation of the endothelial cells lining the sinuses has been previously described, and was observed in this case. Whether these appearances represent actual formation of blood monocytes or not is not demonstrated conclusively, but it seems clear that the major part of the proliferation must take place elsewhere, probably in the reticulum. In many cases, but not in all, some associated myelocytic hyperplasia occurs, and occasionally it may come to dominate the picture. Such observations need not preclude the acceptance of monocytic leukemia as a distinct system disease. Any profound disturbance of one portion of the hematopoietic system interferes with and perverts the activity of the other parts to some extent, a fact which may be explained by the proximity of the precusors of the different types of cells to one another, as well as by their close biologic relationship.

AUTHOR'S SUMMARY.

Microbiology and Parasitology

POLIOMYELITIS APPARENTLY DUE TO A STREPTOCOCCUS IN MILK. E. C. ROSENOW, J. Infect. Dis. **50**:377, 1932.

A study of an epidemic of acute poliomyelitis at a midwestern college is reported. A pleomorphic streptococcus having a peculiar infecting power, specific immunologic properties and characteristic cataphoretic velocity was isolated at the time of the epidemic from the throats and spinal fluid in frank and abortive cases, from the throats of a large portion of well students and from the milk of healthy cows in the dairy, but not after the epidemic had subsided and not at the time of the epidemic or later from the throats of student volunteers, or from the milk supply at a neighboring, unaffected college. The epidemic was traced to

raw milk from which large number of the "poliomyelitis" streptococci were isolated. New cases abruptly ceased to occur after the use of the raw milk was discontinued. There occurred a marked reduction of positive cutaneous reactions to the "poliomyelitis" streptococcus in patients during convalescence and in the well students, especially the men, six weeks after the epidemic had subsided, whereas the incidence remained the same in the students at the unaffected college at the time of the epidemic and six weeks later. The serum of persons who reacted negatively to intradermal injections of the "poliomyelitis" streptococcus, irrespective of whether they had had poliomyelitis, and the poliomyelitis antistreptococcus serum used in treatment neutralized the toxigenic substance to a greater degree than the serum of persons who reacted positively and the serum of the normal horse. The serum from the convalescents and that from persons who had had poliomyelitis a long time before had a more marked specific potential-lowering effect on the "poliomyelitis" streptococcus than the serum of persons who had not had poliomyelitis. The poliomyelitis antistreptococcus serum seemingly had a beneficial action in the treatment of the patients.

AUTHOR'S SUMMARY.

LACTOBACILLUS ACIDOPHILUS IN ADULTS. N. KOPELOFF, N. BLACKMAN and B. MCGINN, J. Infect. Dis. **50**:426, 1932.

Within the limitations of the material, 208 subjects, and of the methods under consideration, it was found that of 187 patients with mental disease, 62 per cent harbored L. acidophilus. The incidence of this organism was slightly higher in the psychogenic than in the somatogenic syndromes. Of 21 nonpsychotic adults, 48 per cent showed L. acidophilus. There is no correlation between constipation and absence of L. acidophilus in fecal specimens. L. acidophilus was found in 64 per cent of the constipated patients with mental disease and in 65 per cent of the nonconstipated patients.

AUTHORS' SUMMARY.

AN EPIDEMIC OF CROUPOUS PNEUMONIA CAUSED BY PNEUMOCOCCUS, TYPE I. A. STRØM, J. Infect. Dis. **50**:430, 1932.

An epidemic of lobar croupous pneumonia in an orphanage was caused by Pneumococcus, type I. Pneumococcus, type I, was found in the sputums and in cultures from the noses and throats of the patients during illness and up to seventy-three days after the crisis. In one case, it was found in a culture from the nose and throat four days before the onset of the disease. Of the contacts, 33.3 per cent were found to be carriers during the height of the epidemic, and 16.9 per cent, two and one-half months later. The strains from the patients were more virulent in mice than those from the carriers. The disease was more prevalent among the older boys than among the younger ones, presumably because the former represented a more rural population than the latter.

AUTHOR'S SUMMARY.

SPOROTRICHOSIS: ITS TRANSMISSION TO PLANTS AND ANIMALS. R. W. BENHAM and B. KESTEN, J. Infect. Dis. **50**:437, 1932.

Sporotrichum schenckii produced in the monkey a nodular sporotrichosis simulating the lymphangitic type of infection in man. The human disease was transmitted to carnations, in which it produced a bud rot similar to that caused by S. poae. After living saprophytically or parasitically in plants, S. schenckii retained its virulence for animals.

AUTHORS' SUMMARY.

AN ORGANISM INTERMEDIATE BETWEEN BACILLUS TYPHOSUS AND BACILLUS DYSENTERIAE SHIGA FROM ATYPICAL TYPHOID FEVER. A. H. LAZERE and V. BREAKS, J. Infect. Dis. **50**:473, 1932.

A bacillus was isolated from the blood of two children in the same family, who apparently had the same infection, an atypical typhoid fever. Bacteriologically and

serologically, this bacillus was intermediate in its characteristics between the typhoid bacillus and the Shiga dysentery bacillus. AUTHORS' SUMMARY.

NONSPECIFIC ORCHITIS AND KERATITIS IN EXPERIMENTAL SYPHILIS. E. E. ECKER and L. A. WEED, J. Infect. Dis. **50**:484, 1932.

In the course of transfers of testicular tissues containing Spirochaeta pallida from rabbit to rabbit, a spontaneous orchitis occurred, which was caused by an organism classified as Bacillus proteus (H type). In some animals, S. pallida co-existed with B. proteus. The disease could be carried from rabbit to rabbit, and the serums of the infected rabbits agglutinated the proteus organisms in high dilutions. Histologically, the picture of the disease was one of massive coagulation necrosis, with thrombosis of the arteries and veins and infiltration of the tissues by polymorphonuclear and mononuclear leukocytes. Noguchi hoped that transplantation of human syphilitic tissue into the testes of rabbits would in a few passages clear the spirochetes from concomitant organisms. But this purification is not readily attained. Caution is urged in the interpretation of results obtained with the so-called pure cultures of S. pallida. AUTHORS' SUMMARY.

DISSOCIATION OF STREPTOCOCCUS CARDIOARTHRITIDIS. N. C. STYRON and S. SPICER, J. Infect. Dis. **50**:490, 1932.

The work on microbic dissociation reported in this paper has been done with the R_1 and R_9 strains of S. cardioarthritidis isolated by Small from blood cultures of patients with rheumatic fever. Fifty cubic centimeter volumes of phosphate broth, with or without dextrose, enriched with 2, 5 and 10 per cent concentrations of peptone, support dissociation. The percentage of peptone most favorable to the process is 5. Strain R_9 is much more unstable than strain R_1. As a result of dissociation, two culture types have been obtained for each strain. The original, or fine, form has been called typical (T). The new, or coarse, form has been designated atypical (A). These T and A forms show distinct and characteristic differences in colony form, in cell morphology and in type of growth in fluid mediums. Cultivation of A and T types in fluid mediums readily causes in R_9 the reversion of A to T. A partial change from T to A in the same strain is sometimes accomplished, but it is very infrequent. In R_1, with the exception of the original T to A transformation in 50 cc. of dextrose phosphate broth, dissociation is only in one direction, A to T. The conversion of A to T is rare. So far as tested, no qualitative difference in carbohydrate fermentation, in action on milk or in production of indol between the T and A forms of homologous strains has been demonstrated. The differences in reaction between the strains are identical with those demonstrated by Small. No tendency to form methemoglobin was evidenced in any of the types either on streak or on pour plates, or by tube hemolysin test. Even after prolonged cultivation in veal infusion broth, no effect on the blood cells was demonstrated. Intradermal tests in rabbits to determine the allergic capacity of T and A types resulted in lesions having distinct characters. The tests with R_1 were insufficient on which to form well grounded conclusions. If the ability to produce the secondary reaction is a reliable index of the allergic potentiality of a given stain, R_9A was a more effective agent than R_9T. If other factors, such as intensity and duration of the secondary reaction, serve as indexes, the results are confusing, and conclusions as to the capacities of the types as allergizing agents can hardly be drawn. The antigenic relationship of the two strains of S. cardioarthritidis has been determined: R_9 is a subtype of R_1, according to the reciprocal agglutinin-absorption reaction; the typical variant R_1T is antigenically identical with the original R_1 strain; R_1A, the atypical dissociated variant of R_1, shows a loss of some antigenic substance and a gain of newly acquired antigenic fractions. The typical, as well as the atypical, variants of strain R_9 cross-absorb with each other and with the original strain, which proves them to be antigenically identical. This, in addition to the fact that they easily

revert to the original smooth form, and also the fact that they give uniform suspensions in saline solution, suggests that they are not true variants, but are possibly in a transitional stage. R_1A, the dissociated variant of strain R_1, and strain R_6, exhibit a common antigenic fraction not found in strain R_1, suggesting the "serologic cosmopolitanism" of the R type. AUTHORS' SUMMARY.

THE GROWTH OF ERYSIPELAS AND SCARLET FEVER STREPTOCOCCI ON HEMOGLOBIN CHOCOLATE AGAR. C. C. SAELHOF, J. Infect. Dis. **50**:536, 1932.

The differences described by Tunnicliff in the color of the colonies of erysipelas and scarlet fever streptococci on blood chocolate agar appear to be due to differences in the effects on the hemoglobin. AUTHOR'S SUMMARY.

FILTER-PASSING ANAEROBIC BACTERIA OF THE NOSE AND THROAT IN HEALTH AND IN COLDS. W. C. NOBLE, JR., and D. H. BRAINARD, J. Prev. Med. **6**:1, 1932.

We have studied the anaerobic bacteria found in the filtered washings of the noses and throats of fourteen persons with colds and eleven normal persons. The ordinary aerobic flora, which, as we have shown in an earlier paper, may grow anaerobically and obscure some of the more slowly growing anaerobes, was removed by using Berkefeld filters of the coarser grades. This procedure also removed anaerobic gram-negative cocci of the gazogenes types, which we had found previously to be normal flora. Many anaerobic bacteria were isolated from the filtrates. Most of these were gram-negative, but there were a few gram-positive forms. We have studied 114 strains, 73 being grouped tentatively according to their agglutinative reactions. The gram-positive flora, isolated from one patient without acute catarrhal coryza, consisted of two strains of bacilli, identical culturally and agglutinatively, and one strain of cocci. The gram-negative flora was much more numerous, our search disclosing minute cocci (not M. gazogenes) and bacilli of different sizes and forms. The cocci were similar culturally, but of four groups agglutinatively. The bacilli were even more heterogeneous, falling into several cultural and agglutinative groups; all were distinct from B. pneumosintes, which we were unable to find. These groups were distributed with approximately equal frequency among both normal control subjects and persons with colds. As to the significance of these findings, the fewness of strains of the gram-positive group and their demonstration in only one subject would weigh against their having a primary etiologic relationship. The almost universal occurrence of the gram-negative cocci and their innocuousness when injected into rabbits would indicate that they are normal saprophytic flora. The heterogeneity of the gram-negative bacilli, the approximately equal distribution of their groups among normal subjects and the persons with colds, and the absence of epidemic strains would make it unreasonable to assign a causative rôle to any one of these organisms, even though it is apparent that pathogens exist among them.

AUTHORS' SUMMARY.

PASSAGE OF POLIOMYELITIS VIRUS THROUGH THE INTESTINAL TRACT. P. F. CLARK, D. J. ROBERTS and W. S. PRESTON, JR., J. Prev. Med. **6**:47, 1932.

We have failed to produced poliomyelitis in monkeys (Macacus cynomolgus) by the oral administration of large quantities of virus or by the injection of 10 cc. of virus into a loop of the small intestine. Infective quantities of virus have been demonstrated in the feces (from 1.5 to 3.5 Gm.) from monkeys that had been infected in various ways. . . . Attempts to demonstrate the virus in the feces of animals suffering from the disease proved futile.

FROM AUTHORS' SUMMARY.

EFFECTS OF THE INJECTION OF NORMAL BRAIN EMULSION INTO RABBITS. E. WESTON HURST, J. Hyg. **32**:33, 1932.

The introduction parenterally into rabbits of emulsions of normal brain tissue is followed by severe toxic manifestations leading to wasting and death. In a few cases, paralyses occur, but similar nervous symptoms have been encountered in other work not involving the use of brain emulsions; the cause of these paralyses has not been determined, and histologically no lesions in the central or peripheral nervous system have been detected. There is insufficient evidence to warrant the view that the paralytic accidents of antirabic treatment are directly due to the foreign nervous substances injected. AUTHOR'S SUMMARY.

STRUCTURAL CHANGES IN THE SPLEEN OF RATS IN STREPTOCOCCAL INFECTION. J. W. ORR, J. Path. & Bact. **35**:149, 1932.

A histologic account is given of the splenic reaction in rats infected with various strains of hemolytic streptococci. The earliest changes are observed in the lymphoid and reticulo-endothelial elements, and these appear to precede any demonstrable infiltration of the spleen by polymorphonuclear leukocytes. The greatest primary activity is found in the perimalpighian zone, at the boundary between the lymphoid follicles and the pulp. Proliferation of reticulum cells with disappearance of lymphocytes is followed by marginal accumulation of neutrophilic leukocytes. When the animal dies — in all cases with streptococcal septicemia — focal necroses are found in the perimalpighian region. Subsequent changes in the pulp are congestion, infiltration by polymorphonuclear leukocytes and multiplication of reticulum cells and later of lymphocytes and plasma cells. There is progressive decrease in the size of the malpighian bodies. Some of the macrophages may be derived from lymphocytes. AUTHOR'S SUMMARY.

FOOT-AND-MOUTH DISEASE LESIONS IN THE EAR EPIDERMIS OF INOCULATED GUINEA-PIGS. T. HARE, J. Path. & Bact. **35**:291, 1932.

The persistence of the virus of foot-and-mouth disease in the epidermis of the ear of the guinea-pig to at least the tenth day after infection is associated with the presence of specific microscopic lesions to the eleventh day after infection. The formation of the initial lesion continues from the second to the fifth day after infection as a characteristic degeneration of a single cell of the stratum germinativum. The formation of vacuoles and vesicles continues from the third to the seventh and from the fifth to the eighth days, respectively. The vesicular exudate is discharged from the fifth to the eleventh day. The stages in the development of a single lesion appear to occupy from three to six days. AUTHOR'S SUMMARY.

THE TRINIDAD OUTBREAK OF ACUTE RABIC MYELITIS. E. W. HURST and J. L. PAWAN, J. Path. & Bact. **35**:301, 1932.

Experimental work is detailed, proving that the cause of the Trinidad outbreak of acute myelitis in man, and of the so-called botulism in cattle, is the virus of rabies. The vector has not been determined with certainty, but the evidence available suggests that it is the vampire-bat. The tissue changes in spontaneous cases and those produced experimentally in the monkey and the rabbit are described. AUTHORS' SUMMARY.

THE ISOLATION OF MOTILE ORGANISMS FROM APPARENTLY NON-MOTILE CULTURES OF B. TYPHOSUS, ETC. D. B. COLQUHOUN and J. KIRKPATRICK, J. Path. & Bact. **35**:367, 1932.

Many organisms that are nonmotile when grown in the ordinary fluid or solid mediums develop motility, when grown on semisolid mediums, e. g., one containing 0.3 per cent agar plus 5 per cent gelatin. Motile strains have been

recovered in this way from nonmotile cultures of B. typhosis, B. proteus, the Salmonella group, B. pestis, B. mallei, B. melitensis, etc. In certain cases—e. g., that of B. typhosus from the feces of a chronic carrier—the original nonmotile cultures, when strained for flagella, showed the presence of such structures in abundance. In other cases—e. g., that of B. suipestifer—flagella were extremely scanty, only a few bacilli showing each a single flagellum. In others, again, no flagella could be demonstrated—e. g., the O variants of B. proteus X 19 and B. melitensis. Certain nonmotile strains of B. typhosus, B. pestis, B. dysenteriae Shiga, B. dysenteriae Flexner-Y, etc., failed to develop flagella and motility after repeated subculturing in semisolid mediums. A satisfactory explanation of the phenomenon described has not been obtained. But the evidence suggests that the development of flagella and motility depends on a suitable viscosity of the medium in which the organisms are growing.

AUTHORS' SUMMARY.

THE INTERSTITIAL REACTIONS CAUSED BY VARIOUS DUSTS AND THEIR INFLUENCE ON TUBERCULOUS INFECTIONS. E. H. KETTLE, J. Path. & Bact. **35**:395, 1932.

Suspensions of silicious and nonsilicious dusts were injected subcutaneously into mice; into the lesions caused by the injected dusts tubercle bacilli were subsequently injected, and their growth studied. The silicious substances, except carborundum, caused necrosis with cellular reaction and favored growth of the tubercle bacilli; the nonsilicious dusts were inert and did not favor the growth of tubercle bacilli. The suggestion is made that the method outlined may be of value in determining whether or not certain industrial pollutions of the atmosphere are dangerous.

THE CAUSATIVE ORGANISM IN INFECTIOUS ECTROMELIA. J. E. BARNARD and W. J. ELFORD, Proc. Roy. Soc., London, s. B. **109**:360, 1931.

From mice infected with the virus of infectious ectromelia, minute bodies have been obtained, both from characteristic inclusion bodies and by differential filtration of infective organ extracts, which are shown, in ultraviolet photomicrographs, to be minute, coccoid micro-organisms. Evidence is given that these organisms are the virus.

AUTHORS' SUMMARY.

Immunology

ANTIPNEUMOCOCCIC REACTIONS BY HUMAN BEINGS. W. D. SUTLIFF and M. FINLAND, J.Exper.Med. **55**:837 and 853, 1932.

The incidence of pneumococcidal power of the whole defibrinated blood in human beings has been shown to vary with age. The age distribution of other type-specific antibodies varies similarly, so far as they are frequent enough to be compared or technically demonstrable. The incidence of pneumococcidal power of the whole defibrinated blood for type I, type II and type III differs. Type I is the rarest, type II is the most frequent, and type III is of intermediate frequency. The type-specific antibodies responsible for the other tests employed show a similar relative frequency in regard to types I and II, but some variation in regard to type III. The skin reactions to the acetic acid-precipitable proteins and autolysates of the pneumococci are negative or rarely positive in infants, infrequently positive in childhood and positive in a high percentage of adults.

The blood of sixty-three human subjects selected because of the absence of recent infections was studied for its content of specific antibodies against virulent strains of type I, II and III pneumococci before and after intracutaneous injections of minute amounts of pneumococcal products. The simultaneous injection of the specific polysaccharides of all three types of pneumococci and of proteins and autolysates derived from type I and II pneumococci was followed by the appearance or increase of pneumococcidal power in the whole defibrinated blood

and, in most instances, by the appearance of mouse-protective antibodies and agglutinins for one or more types. A single intracutaneous injection of 0.01 mg. of the protein-free, type-specific polysaccharide of type I, type II or type III pneumococci or four similar daily injections were followed, in most of twenty-nine subjects, by the appearance of antibodies against the homologous, but not against the heterologous, type pneumococci. Some subjects showed a simultaneous lowering of a preexisting pneumococcidal power for heterologous or homologous types. A single intracutaneous injection of 0.1 mg. of pneumococcus protein in thirteen persons was not followed by the appearance of specific antibodies to any appreciable degree. Single intracutaneous injections of small amounts of autolysates derived from virulent strains of type I, II or III pneumococci were followed in eleven subjects by a more or less general rise in the pneumococcidal power, with the appearance of homologous type agglutinins and protective antibodies in about one third of the subjects.

AUTHORS' SUMMARY.

ANTIPNEUMOCOCCUS PROPERTIES OF NORMAL SWINE SERUM. W. H. KELLEY, J. Exper. Med. **55**:877, 1932.

Normal swine serum possesses, in low degree, type-specific protective properties against pneumococci, like a polyvalent antipneumococcus serum produced by artificial immunization. These protective properties are destroyed by heating at 65 C. When the serum is mixed with purified type-specific polysaccharide, precipitation or fixation of complement does not result, and the protective action is not inhibited by homologous polysaccharide. Swine serum causes agglutination of avirulent R pneumococci, and this property is not destroyed by heating at 65 C.

ANTIPNEUMOCOCCI REACTIONS OF RABBITS. L. A. JULIANELLE and M. C. MORRIS, J. Exper. Med. **55**:867, 1932.

Following repeated intracutaneous injections of heat-killed S or R pneumococci, rabbits acquire an increased skin reactivity to the nucleoprotein of both Pneumococcus and indifferent Streptococcus. Rabbits acquire a skin reactivity to the proteins of both the organisms mentioned after receiving intracutaneous injections of heat-killed indifferent streptococci. Injections of pneumococci into the skin are followed in some rabbits by an eye sensitivity to pneumococcus protein but not to streptococcus protein or to suspensions of either living organism. Injections of indifferent streptococci into the skin are followed, in some rabbits, by an eye sensitivity to suspensions of live indifferent Streptococcus but not to R Pneumococcus or to the nucleoprotein of either organism. Measured in terms of bacterial specificity, therefore, the eye sensitivity possesses a specificity which is not shared by the skin sensitivity. The serums of rabbits given intracutaneous injections with pneumococci or indifferent streptococci contain agglutinins for both R Pneumococcus and indifferent Streptococcus. Only those animals given injections of pneumococci acquire resistance to pneumococcal infection.

AUTHORS' SUMMARY.

ACTIVE IMMUNITY TO LOCAL SKIN REACTIVITY TO BACTERIAL FILTRATES. G. SHWARTZMAN, J. Exper. Med. **55**:889, 1932.

Spontaneous active immunity to the phenomenon of local skin reactivity to bacterial filtrates has been demonstrated. In one experiment, the immunity was nonspecific, while in others it appeared limited to one or two bacterial species. Intradermal vaccination of rabbits with bacterial filtrates induced active immunity to the phenomenon. The specificity of this immunity was tested with graded amounts of toxic factors. The combined intradermal and intravenous immunization in these experiments elicited two types of response: specific immunity, which was obtained in rabbits highly susceptible to the phenomenon (i. e., showing reactions with 1 reacting unit), and nonspecific immunity, which was elicited in rabbits with partial spontaneous immunity (i. e., showing no reactions with 1

reacting unit, but susceptible to 15 units one week later). Comparative studies on the reacting potency of "agar washings" and disintegrates (Besredka's method, and a freezing and thawing method) showed that the first washings of bacterial cells are considerably stronger than subsequent washings and disintegrates. These facts demonstrate once again the extracellular nature of the material necessary for the phenomenon. Tentative explanations of the mechanisms involved in the specific and nonspecific immunity to the phenomenon are discussed.

AUTHOR'S SUMMARY.

THERAPEUTIC VALUE OF TYPE I PNEUMOCOCCUS ANTISERUM. T. J. CURPHEY and H. B. BARUCH, J. Exper. Med. **55**:925, 1932.

Intramuscular dosage of antipneumococcal serums in a standard dermal pneumococcic infection in rabbits is as effective as intravenous dosage, provided the degree of blood stream invasion is not unusually high. The immediate bactericidal effect of doses of serum given intramuscularly is equal to that of the same doses given intravenously in the cases of mild and moderately severe bacteremias. The intramuscular method of serum administration in human beings with lobar pneumonia deserves a carefully controlled clinical trial.

AUTHORS' SUMMARY.

VACCINATION AGAINST YELLOW FEVER WITH IMMUNE SERUM AND VIRUS FIXED FOR MICE. W. A. SAWYER, S. F. KITCHEN and W. LLOYD, J. Exper. Med. **55**:945, 1932.

After preliminary experiments on monkeys, fifteen persons were actively immunized by a single injection of a dried mixture of living yellow fever virus, fixed for mice, and human immune serum, with separate injections of enough additional serum to make up the amount required for protection. One person was similarly immunized by injecting immune serum and dried virus separately. By titration of the serums of vaccinated persons in mice, it was shown that the immunity rose in a few weeks to a height comparable to that reached after an attack of yellow fever, and remained there throughout an observation period of six months. Yellow fever virus could not be recovered from the blood of vaccinated persons or monkeys, except when the latter had received less than the amount of immune serum required for the minimal effect. Neutralization of yellow fever virus by immune serum took place very slowly in vitro at room temperature in our experiments, and could not have been an appreciable factor in vaccination with the serum virus mixtures. A mixture of fixed virus and immune serum retained its immunizing power for eight months when dried in the frozen state and sealed in glass. It appears that the immunizing reaction after yellow fever vaccination was a part of a true infectious process, as was also the leukopenia.

AUTHORS' SUMMARY.

IMMUNIZATION OF CHIMPANZEES WITH HUMAN BLOOD. K. LANDSTEINER and PHILIP LEVINE, J. Immunol. **22**:397, 1932.

A remarkable feature of the experiments was the easy production of agglutinins after injection of human blood into chimpanzees. Using as a criterion the results of serologic tests, the difference between human blood and blood of the same group from chimpanzees is less pronounced than that between human blood of different groups. Yet, from the experiments reported by Thomsen, who injected blood B into persons of group A and vice versa, one may conclude that in human beings group specific immune antibodies are formed with difficulty. Granting that the same rule holds for chimpanzees, the reason for the effect of immunization is, in all likelihood, the difference in species between human and chimpanzee cells. It would seem plausible that in respect to this the protein components of the red cells play a significant rôle, so that a slight difference between them would suffice for the production of antibodies, the similarity of the haptens notwithstanding.

AUTHORS' SUMMARY.

ANAPHYLAXIS TO DIPHTHERIA TOXIN FROM PLACENTAL TRANSMISSION OF ANTITOXIN. J. Y. SUGG, L. V. RICHARDSON and J. M. NEILL, J. Immunol. **22**:401, 1932.

The offspring of antitoxic, immune guinea-pigs showed anaphylaxis when given intravenous injections of a toxin-containing material from thirty to sixty days after birth. Sufficient controls were made on the possibility of participation of nontoxic antigens and of nonantitoxic antibodies to justify the conclusion that the anaphylaxis was due to reaction between the toxic antigen and the placentally transmitted antitoxin. The advantage of the use of carefully selected offspring was demonstrated by the high degree of completeness of nonreactivity to nontoxic diphtheria antigens that was exhibited by the offspring of individual mothers with serum containing none or only small amounts of diphtheria antibodies other than antitoxin. Apart from the question of toxin anaphylaxis, the present demonstration of anaphylaxis to diphtheria material on the part of the offspring of immune guinea-pigs is of interest as an example of placental transmission of hypersensitiveness to an antigen of bacterial origin.

AUTHORS' SUMMARY.

IMMUNOLOGICAL STUDIES IN TUBERCULOSIS. S. A. PETROFF, W. STEENKEN, JR., and W. A. WINN, J. Immunol. **22**:413, 1932.

The skin of chickens can be rendered hypersensitive with heat-killed avian tuberculosis bacilli. Those whose skin had been sensitized with heat-killed R showed a greater tuberculin hypersensitiveness. In those sensitized with heat-killed S a greater degree of protection to a subsequent infection with living virulent avian bacilli and less hypersensitiveness to tuberculin developed. The experiments suggest the possibility of vaccinating fowls against avian tuberculosis.

AUTHORS' SUMMARY.

SPECIFIC THERAPY OF PNEUMOCOCCUS CARRIERS. F. NEUFELD and R. ETINGER-TULCZYNSKA, Ztschr. f. Immuntätsforsch. u. exper. Therap. **74**: 160, 1932.

Mice and guinea-pigs were infected with pneumococci types I and II, and became carriers by instillation of a culture into their nostrils or by contact with carriers. Prophylactic active and passive immunization protected mice against a generalized fatal infection but did not prevent them from becoming pneumococcus carriers. Guinea-pig pneumococcus carriers were not benefited locally by systemic specific treatment with intraperitoneal injections of immune serum; local applications of the serum markedly diminished the number of bacteria in the nasal secretions, and a combined general and local treatment caused a complete disappearance of the bacteria from the infected mucous membranes. The effect of such treatment was beneficial also in mice, but not so marked as in guinea-pigs. Mice carriers were not benefited by injections of optochin and by local applications of optochin and acriflavine. Guinea-pig carriers were not improved by local applications of optochin and hydrogen dioxide. Infants suffering from infections of the upper respiratory tract due to pneumococci did not respond to local applications of optochin.

I. DAVIDSOHN.

SO-CALLED SUBGROUPS OF A. ALFRED KLOPSTOCK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **74**:211, 1932.

For the differentiation of the subgroups A_1 and A_2 certain antisheep immune serums can be employed, provided they agglutinate specifically the human red cells A. Also other A-specific hetero-agglutinating serums can similarly be used, for instance, some normal rabbit serums and rabbit immune serums, following injections of human red cells A. They replace well for that purpose the iso-agglutinating serum anti-A. The Forssman antigen is present in both subgroups.

The differentiation can also be accomplished with the help of complement fixation, A-antiserums and hemolysed red cells or alcoholic red cell extracts being used as antigens.

I. DAVIDSOHN.

CHEMICAL AND PHYSICOCHEMICAL CHANGES IN THE BLOOD SERUM FOLLOWING INFECTION AND IMMUNIZATION. T. WOHLFEIL, Ztschr. f. Immunitätsforsch. u. exper. Therap. **74**:229, 1932.

Subcutaneous and intravenous injections with Staphylococcus aureus were used. The subcutaneous injections produced mild lesions. The intravenous injections led to death in about thirty hours, unless a nonspecific resistance was produced by feeding large quantities (10 Gm. twice a day) of dextrose, when the animals lived for at least eight to ten days. No significant changes of the kind mentioned in the title were observed in the animals dying from a fulminant toxemia. An increase of tryptophan was found in the electrodialyzed portion of the globulin in rabbits showing a mild local infection, but in those that received injections intravenously but were treated with dextrose there was an increase of the euglobulins and of the tryptophan, while the tyrosine was decreased in the electrodialyzed fraction of the albumin.

I. DAVIDSOHN.

IMMUNITY AGAINST DIPHTHERIA AMONG THE BLACK RACES. OTTO FISCHER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **74**:244, 1932.

Among 283 natives of East Africa only 3 gave a positive reaction to the Schick test. This was explained by a relatively high titer of diphtheria antitoxin in the blood of those tested, being one twentieth of a unit or more in 73 per cent of them.

I. DAVIDSOHN.

IS THERE A RELATION BETWEEN THE BLOOD GROUP AND MENTAL DISEASES? WALTER SALECK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **74**:280, 1932.

Gundel reported a higher incidence of blood groups B and AB among the inmates of the insane asylums in Schleswig-Holstein than among the normal population. Such a difference could not be found in Württemberg. Neither could deviations from the normal be found when single clinical disease entities were studied from the standpoint of the blood group. The distribution of the blood groups among the urban and the rural population was about the same, which is again contrary to the findings of Gundel.

I. DAVIDSOHN.

MASKING OF ANTIGENIC EFFECTS OF HAPTENS IN VITRO AND IN VIVO INHIBITION OF THE IMMUNOGENIC EFFECT OF CHOLESTEROL BY LECITHIN. F. PLAUT and H. RUDY, Ztschr. f. Immunitätsforsch. u. exper. Therap. **74**:333, 1932.

Cholesterol and alcoholic extracts of various tissues lost the binding ability with their corresponding serum when mixed with lecithin and with alcoholic extracts of certain tissues. Beef heart extract was influenced least of all, and only by lecithin. Alcoholic extracts of Spirochaeta pallida had an inhibiting effect on cholesterol but not on beef brain and beef heart. Cholesterol, which is able to produce specific immune serums in rabbits, lost that ability when it was mixed with lecithin.

I. DAVIDSOHN.

Tumors

ALLERGIC SKIN PHENOMENA IN CONNECTION WITH GENERALIZED LYMPHOSARCOMA. H. AULER, Ztschr. f. Krebsforsch. **34**:228, 1931.

Auler describes peculiar dermographic findings in a case of lymphosarcomatosis, in which, after needle stroking over recent metastatic lesions, there appeared a

white streak surrounded by a diffuse red areola. Over older lesions with cutaneous atrophy, this reaction was absent. Auler ascribes the reaction to the liberation from the tumor, under the pressure of the needle, of substances of basic character; the changes were dissimilar from those produced by histamine.

H. E. Eggers.

Histologic Diagnosis of Tumors by Means of Histochemical Demonstration of Cholesterol. X. Chahovitch, Ztschr. f. Krebsforsch. **34**:258 and 263, 1931.

In these two articles are reported the results of an investigation of the method proposed by Schultz for the diagnosis of malignancy in excised tumors, namely, by microscopic determination of their cholesterol content. Cholesterol as identified by Schultz' method was lacking in all benign tumors, with the exception of two benign hypernephromas and one hard fibroma, and uniformly present in carcinomas, but in sarcomatous tissues it was as a rule lacking. In experimentally induced tar cancers, it was absent during the precancerous stages, but appeared with the onset of infiltrative growth.

H. E. Eggers.

Cancer Metastases in Bone with Special Reference to Osteophytosis. J. Zemgulys, Ztschr. f. Krebsforsch. **34**:266, 1931.

Osteophytosis in cancer begins with metastatic lodgment in spongy bone, with subsequent penetrative growth through the compact portion. Such penetration can occur by growth along vascular channels, as a result of atrophy of the compact bone, or by erosion of the bone by the tumor. Along with the penetrative growth there is transportation of bone-forming cells, which, on reaching the surface, produce the bony excrescences.

H. E. Eggers.

Production of Experimental Sarcoma in the Rat. C. M. Bellows, Ztschr. f. Krebsforsch. **34**:348, 1931.

In this article are described some interesting results obtained by repeated injections of fresh tomato juice intraperitoneally into rats. With great regularity, peritoneal sarcomatosis developed, and with a B. subtilis-like organism isolated from the tomatoes, a similar effect was obtained. Tomatoes from a wide geographic range showed identical results.

H. E. Eggers.

Sarcoma of the Rat from External Agencies. M. Askanazy, Ztschr. f. Krebsforsch. **34**:362, 1931.

Askanazy repeated the experiments of Bellows in modified form, using only single injections of tomato juice, or of the organisms obtained from it, in conjunction with rat embryonic tissue. Just as did Bellows, he obtained peritoneal sarcoma with practically constant regularity.

H. E. Eggers.

Diffuse Carcinomatosis of the Peritoneum. B. P. Abramsohn, Ztschr. f. Krebsforsch. **34**:382, 1931.

A case is reported of gastric cancer that showed widespread diffuse peritoneal carcinomatosis and fibrosis, without metastatic involvement elsewhere. There is included a discussion of the differential diagnosis of this unusual form of cancerous spread.

H. E. Eggers.

Attempts at the Early Diagnosis of Cancer by Capillary-Dynamic Methods. W. Kaelin, Ztschr. f. Krebsforsch. **34**:457, 1931.

There is here described a tentative method for the early diagnosis of cancer by means of alterations in capillary behavior of whole blood. This is diluted,

subjected to capillary rise in filter paper, and this, after drying, is immersed in solution of various vegetable extracts to obtain a second capillary effect. Kaelin states that in about 700 tested cases, 75 per cent of those of early carcinoma showed a characteristic reaction — a cauliflower-like margin of capillary rise, as compared with the fairly even margin shown by other specimens.

H. E. Eggers.

So-Called Hemangio-Endothelioma of the Liver. L. Puhr, Ztschr. f. Krebsforsch. **34**:503, 1931.

Puhr reports a case of so-called hemangio-endothelioma involving the liver and the pancreas. These organs were studded with colonies of large, pale-staining cells which frequently had foamy cytoplasm and occasionally showed phagocytic action. On morphologic grounds, he considers that these cells are derivatives of capillary linings; he regards their wide distribution in the involved organs as being the result of diffuse action of the same cancerigenic agent, rather than as metastases.

H. E. Eggers.

A Comparative Statistical Study of Gastric Cancer. W. Cramer, Ztschr. f. Krebsforsch. **34**:531, 1931.

This is a stimulating and interesting contribution to the statistical literature on cancer. Cramer points out that cancers of some one system may occur in two populations in widely different proportions, without the occurrence of any identifiable environmental features to explain the difference. If, however, one accepts the postulate that the total mortality from cancer in a given population may be accepted as an expression of the cancerous potentialities of that population — as an index to the proportion of persons with cancerous predisposition — then the incidence of cancer of any one system will be determined by two factors, indirectly by the relative frequency of other cancers, directly by the action of cancerigenic irritants. Where the systemic incidence of cancer is regulated largely by the indirect factor, search for environmental agencies will, of course, be fruitless. To determine whether statistical study would reveal evidence of the direct factor, Cramer has made a comparison of the mortality from gastric cancer in England and, principally, Bavaria. In the former country, carcinoma of the stomach constitutes only 22.2 per cent of the cancers in males; in the latter country, 55.8 per cent. With females, the relative proportions are 16.6 per cent and 42.3 per cent. On investigation of the distribution of these cancers by occupation, it is found that in Bavaria cancer of the stomach is outstandingly a disease of farmers, artisans and workmen, with rates ranging from 66 to 70 per cent of all cancers, while in other comparable occupations it forms about 35 per cent. In England, the high incidence in farmers is lacking, and the disease is particularly frequent in miners and stone-masons. But in both countries it shows a peculiarly high incidence among members of the lower social orders — not shown by cancers lower in the alimentary tract. Cramer concludes that here, in the case of Bavaria, and other continental European countries which are considered in less detail, a direct factor of the sort he had postulated is concerned; more detailed study would be necessary to recognize precisely what particular agency is implicated, but its identification would be of extreme value from the point of view of the prophylaxis of cancer.

H. E. Eggers.

The Follicular Hormone Content of the Blood of Male Tumor-Bearing Mice. P. Engel, Ztschr. f. Krebsforsch. **34**:658, 1931.

Laquer and his associates have announced that in the blood of cancerous persons of both sexes there is found a considerable increase of follicular hormone. Engel, testing the blood of male mice inoculated with carcinoma, sarcoma and chondroma, likewise finds that in the animals with carcinoma and sarcoma this hormone was greatly increased; but with the slowly growing chondroma this was not the case.

H. E. Eggers.

THE FIBRIL-PRODUCING POWER OF SARCOMAS. M. GLASUNOW, Ztschr. f. Krebsforsch. **34**:661, 1931.

Basing his conclusions on the study of fifty specimens of sarcomas, Glasunow divides them, with respect to fibrillogenesis, into three main classes. The first class includes sarcomas in which this property is wholly or almost wholly lacking; such tumors were for the most part round cell sarcomas, and their lack of fibrillation may in part be explained by the immature character of the tumor cells; however, among this group may be included tumors other than those derived from fibrous connective tissue, in which case the property would be inherently absent. His second class embraces tumors in which intercellular fibrillar formation is limited to a reticular structure, similar to that of lymphadenoid tissue, and characterized by the formation of anastomosing fibrils. The third class, comprised of spindle cell sarcomas and fibrosarcomas, is characterized by much fibrillar formation in the form of broad, wavy bands, with little or no anastomosis between the elements constituting them. Since such a development represents a relatively mature development of tumor cells, it would be inconspicuous or absent in the more immature types of these tumors. H. E. EGGERS.

THE FREQUENCY OF PULMONARY CANCER. H. BUSCHBECK, Ztschr. f. Krebsforsch. **34**:678, 1931.

At the Johannstadter Krankenhaus at Dresden, primary carcinoma of the lung has been observed, in the years 1923 to 1930, in 19.8 per cent of all autopsies in cases of cancer — a relative incidence hitherto never equaled. In men, these cases comprised 4.21 per cent of all autopsies, and 28 per cent of all cases of malignant growth. The corresponding figures for women were 0.80 and 6.83 per cent. In 1926, the figures were especially remarkable, with corresponding percentages for men of 5.76 and 43.5. The average ages of occurrence were 60 years for men and 59 for women. The right lung was primarily involved with slightly greater frequency, but there was little difference between the upper and lower lobes. While approximately half of the men had occupations associated with inhalation of smoke or dust, and 43.6 per cent had records of previous pulmonary disease, the percentage of smokers among them was 26.9 — no higher than that of the general population. There was an undue frequency of previous rheumatic disease — more so than among cases of cancer in general. H. E. EGGERS.

A CASE OF SARCOMA OF THE TONGUE. H. KUDLICH, Ztschr. f. Krebsforsch. **35**:99, 1931.

There is here described and illustrated, unfortunately only grossly, a case of what would appear to have been a mixed cell sarcoma of the base of the tongue. There was no evident involvement of the cervical glands. H. E. EGGERS.

COMPARATIVE INVESTIGATIONS OF DIFFERENT REACTIONS FOR CARCINOMA. O. SIEVERS, Acta path. et microbiol. Scandinav. **9**:111, 1932.

Various reactions — albumin-A, Roffo, Miostagmin, Freund, Kaminer, complement fixation — were studied with the general result that no one of the reactions can be used safely for the early diagnosis of carcinoma.

PRIMARY MALIGNANT TUMOR OF THE LUNG. E. ASK-UPMARK, Acta path. et microbiol. Scandinav. **9**:159, 1932.

Between 1890 and 1930 forty-four cases of primary malignant tumor of the lung were observed in the pathologic institute of the University of Lund, without any increase in frequency during this period. In order to throw light on the increasing frequency of primary malignant tumor of the lung in recent years, Ask-Upmark recommends that information as free from error as possible should

be obtained from many different sources and studied in some central place, as, for instance, the department of public health of the League of Nations.

THE RELATION OF SO-CALLED ADENOSARCOMA IN THE KIDNEY TO NEUROBLASTOMA. F. HARBITZ, Acta path. et microbiol. Scandinav. **9**:199, 1932.

It is pointed out that certain cases at least of so-called embryonal adenosarcoma of the kidney correspond closely in structure with that of certain forms of neuroblastoma.

Medicolegal Pathology

INJURIES TO THE BONES OF HUMAN CADAVERS BY RODENTS. G. WEYRICH, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:118, 1932.

Parts of a human skeleton were accidentally discovered in a forest. The skull contained many irregularly formed defects and perforations, the edges of which showed small parallel-running double furrows, which corresponded to the gnawing teeth of the rodents living in that particular region. The injuries closely resembled those produced by a heavy jagged instrument or by a chisel.

E. L. MILOSLAVICH.

CHANGES IN THE MAMMARY GLAND PRODUCED BY REMOVAL OF THE NIPPLE. G. BURCKHARD, Frankfurt. Ztschr. f. Path. **42**:494, 1932.

The nipple of a 14-year-old girl was bitten off by a horse. Burckhard, as an expert witness, was asked whether or not complications of the breast might arise during lactation. Realizing the difficulties in answering this question, he resorted to experiments on animals. In a number of female rabbits, the nipples of one side were amputated. The animals were allowed to become pregnant and were killed from 24 to 366 hours after delivery of their litters. Both breasts were examined. The main difference between the side operated on and that not operated on was that the acini of the side operated on initially were wider and the epithelial lining was distinctly lower. There also was a marked stagnation of the secretion. After 288 hours, however, the acini became smaller again, and after 366 hours the difference between the normal breast and that operated on was not significant. Burckhard points out especially that even though the breast operated on, 48 hours after the litter was thrown, was hyperemic grossly, histologically there was no difference between the two breasts.

O. SAPHIR.

CAUSAL RELATION OF TRAUMA TO SARCOMA OF BONE. A. TROELL, Virchows Arch. f. path. Anat. **283**:550, 1932.

Troell's discussion is based on an analysis of 114 sarcomatous and sarcoma-like lesions of long bones. Twenty-eight of these were cases that had been submitted to the governmental bureau of compensation and insurance of Sweden. The gross and microscopic appearances of the lesions were correlated with the history of injury. If trauma is to be considered an etiologic factor in the development of sarcoma of bone, there must be a history of localized injury of severe enough degree to cause local manifestations of trauma, and the injury must be followed within a reasonable time by the development of a sarcoma. Troell admits the possibility that trauma may cause sarcoma of bone, but believes that the relationship can be established with scientific and unquestioned accuracy in only relatively few instances. In cases in which compensation and insurance are involved, it may be necessary to admit that trauma may have been a factor, although the causal relation of the trauma to the tumor may not be proved.

O. T. SCHULTZ.

HISTOLOGIC CHANGES IN THE BRAIN IN EXPERIMENTAL CHRONIC ILLUMINATING GAS POISONING. E. RIX, Virchows Arch. f. path. Anat. **283**:801, 1932.

In an attempt to reproduce the late cerebral lesions of illuminating gas poisoning in man, dogs were subjected to an atmosphere that contained relatively little of the gas. The chamber had an opening that permitted escape of gas and entrance of fresh air. The animals were placed in the chamber daily and allowed to remain until they had just lost consciousness. They were killed after from fourteen days to one year of such daily intoxication. In acute experiments, the only change noted was a narrow zone of hemorrhage about the capillaries. In experiments of longer duration, areas of degeneration were seen about the vessels. Some of the perivascular lesions were infiltrated by colloid material in which there was a granular deposit; this change the author believes to be a precursor of calcium deposition. Some of the perivascular lesions were replaced by proliferated glia. Diffuse gliosis was also noted beneath the ependyma.

O. T. SCHULTZ.

TRAUMATIC LATE APOPLEXY. H. ECK, Virchows Arch. f. path. Anat. **284**:67, 1932.

In a well written article, Eck critically reviews the literature relating to the occurrence of cerebral hemorrhage at an appreciable interval after injury to the head. From 1891, when Bollinger described the symptom complex and pathologic anatomy of this condition, until 1903, when Langerhans subjected the matter to critical revision, nineteen cases were recorded. From 1903 until the present time, in spite of the increasing number of head injuries in civil life and during the World War, only thirteen cases were reported. Eck agrees with those previous writers who maintain that the relation of apoplexy to head injury sustained at an interval preceding the hemorrhage, in a previously normal person, can be established only by the most critical scrutiny of clinical and postmortem findings. He presents a case that he thinks withstands such scrutiny. A laborer, aged 27, fell backward from a step 50 cm. high, striking on the back of the head. He was unconscious for a short time. There was no external evidence of trauma to the head. Following the injury he had almost constant headache, vomited frequently, and was unable to work. He gradually improved and four weeks after the injury returned to work. While he was mounting a stairway after the noon rest period, his gait suddenly became unsteady, and he made his way to the ground, where he fell over unconscious. Cisternal puncture yielded almost pure blood. Death occurred ten hours after the onset of the terminal symptoms. Necropsy revealed an older area of softening in the anterior pole of the left temporal lobe and a recent massive hemorrhage that extended anteriorly into the area of softening and posteriorly into the ventricular system. Microscopic examination revealed autolytic softening of the small blood vessels in the peripheral portion of the area of softening. The vessels elsewhere were normal. There was nowhere any calcification of ganglion cells or capillaries, such as might have resulted from generalized concussion of the brain. Eck interprets the sequence of events as follows: The injury caused contusion of the left temporal lobe by contrecoup. Softening of brain tissue and autolysis of blood vessels followed. During the succeeding period of rest, the weakened vessels were probably occluded by loose thrombi or by collapse of their walls. Return to work and increase in blood pressure led to rupture of the altered vessels and to hemorrhage.

O. T. SCHULTZ.

BRAIN LESIONS OF ACUTE BARBITAL (VERONAL) POISONING. ELSE PETRI, Virchows Arch. f. path. Anat. **284**:84, 1932.

As a rule no characteristic changes are found in the brain after fatal poisoning by barbital and its derivatives. As in many other intoxications, there may be vascular engorgement and stasis, perivascular edema and small perivascular hemor-

rhages. The brain of a man who died three days after taking barbital with suicidal intent revealed more striking alterations. Small perivascular areas of hemorrhage, edema and demyelinization were numerous and were scattered throughout all portions of the brain. The walls of the vessels were normal, but many of them contained small masses of fibrin intermingled with material in the form of droplets. About some of the small vessels were groups of cells filled with fat droplets.

O. T. SCHULTZ.

Technical

A NEW EMBEDDING MATERIAL. S. T. ORTON and J. POST, Bull. Neurol. Inst., New York **2**:302, 1932.

The commercial synthetic soap, glycol stearate, is miscible with water, melts at about 48.5 C. and at room temperature is of excellent consistency for cutting on the microtome. These characteristics enable the embedding of tissues direct from aqueous mediums without the preliminary dehydration required for paraffin and celloidin (a concentrated preparation of pyroxylin). A method for embedding in this material is described, and the results of some preliminary experiments with staining methods applied to sections obtained in this way are recorded.

AUTHORS' SUMMARY.

THE PREPARATION OF A GRADED SERIES OF ULTRAFILTERS AND MEASUREMENT OF THEIR PORE SIZES. A. P. KRUEGER and R. C. RITTER, J. Gen. Physiol. **13**:409, 1930.

The authors prepared a graded series of ultrafilters, impregnating filter paper with glacial acetic acid solutions of negative cotton, in which the latter substance was varied according to the density of the membrane desired. After thorough impregnation, gellation was effected by submersion in sterile water, and all traces of acid were removed by repeated washings. The pore sizes of the entire series were determined by measuring permeability to purified sols of known particle sizes, and the estimates so obtained were compared with pore diameters calculated from data on rate of flow. A constant difference between the two sets of figures was observed, the pore diameter for any given membrane as estimated by permeability to sols being some 150 millimicrons less than that calculated from data on permeability to water.

The membranes are useful in determining the particle size of ultramicroscopic viruses. They require no sterilization and are employed in connection with a simple glass ultrafilter apparatus described in detail in the paper.

A. P. KRUEGER.

THE MICROSCOPIC SLIDE PRECIPITATION TEST FOR SYPHILIS WITH SPINAL FLUID. J. J. ELLER and C. R. REIN, New York State J. Med. **32**:71, 1932.

The microscopic slide precipitation test [Kline] with spinal fluids has been found to be more sensitive than the Wassermann reaction, modified Kahn test, colloidal gold reaction and albumin-globulin ratios. This test gave results that agreed more frequently with the clinical condition of the patients than did those of the other spinal fluid tests used in this series. The test is simple in detail, and the results magnified by the microscope are read accurately with ease.

AUTHORS' SUMMARY.

THE FRIEDMAN MODIFICATION OF THE ASCHHEIM-ZONDEK PREGNANCY TEST. ALBERT MATHIEU, ALLAN PALMER and ALBERT HOLMAN, Northwest Med. **31**:215, 1932.

Mathieu and his associates use virginal female rabbits 12 to 14 weeks old. Their rabbit-raiser separates the animals from their litter-mates three months after the

date of their birth and brings them to the laboratory as needed. A rabbit at any age older than 3 months may be used, but if older than about 4½ months, care must be taken to isolate the animal from the male for thirty days before it is used. The gestation period in a rabbit being thirty-one days, it is easy to determine in about three or four weeks' time by palpation whether the female has or has not been exposed to the male. The specimen of urine is collected at any time during the day, preferably in the morning, acidified with 10 per cent acetic acid and treated with toluene (1 drop to 50 cc. of urine). Depending on the concentration of the urine, from 10 to 17 cc. is slowly injected into the ear vein of the rabbit, from three to five minutes being taken to make the injection. In not a single instance in their series of 110 cases has the urine caused the death of the rabbit. The rabbits are killed after thirty-six hours, and each ovary is examined. The results of the rabbit test in the hands of the authors were "highly gratifying" for the recognition of early pregnancy and for differential diagnostic purposes. The relatively low cost, the saving of time, and the ease with which the results are determined recommend the Friedman modification of the Aschheim-Zondek test.

I. DAVIDSOHN.

TAKAYAMA'S SOLUTION IN THE IDENTIFICATION OF BLOOD STAINS. A. V. GREAVES, Brit. M. J. **1**:932, 1932.

Takayama's solution is recommended as a simpler and more reliable test for blood than the older and more generally used hemin test. It is essentially a test for hemochromogen. The method is as follows: Add a drop of the solution (3 cc. of pyridine, 3 cc. of saturated dextrose solution, 3 cc. of 10 per cent sodium hydroxide and 7 cc. of distilled water) to a scraping of the suspected material on a glass slide, adjust the cover-slip and examine under the microscope. If blood is present, reddened areas appear in which pinkish, flat, rhomboid crystals of hemochromogen will be observed to form. The ends of individual crystals often appear splintered. High magnification is necessary. If the reddened areas are immediately observed through a hand spectroscope, the characteristic absorption bands of hemochromogen are discernible.

C. A. JOHNSON.

NEW METHOD FOR OCCIPITAL PUNCTURE IN THE RABBIT. Z. OHYA, J. de physiol. et de path. gén. **29**:518, 1931.

Puncture with a needle between the occipital bone and the posterior tubercle of the atlas in a rabbit yielded spinal fluid, drop by drop, and from 0.8 to 1.5 cc. was obtained at various times by gentle aspiration with a syringe. After one week, fourteen times the amount of fluid could be taken without causing death. In experiments with more than one hundred rabbits there were six deaths. Three deaths occurred during the experiments and the other three one week after the operation.

H. S. THATCHER.

NEW RAPID STAINING OF TUBERCLE BACILLI IN SPUTUM. P. DOGLIO, Gior. di batteriol. e immunol. **8**:243, 1932.

Doglio spreads the material on a slide and applies Ziehl's carbolfuchsin, heats the slide until it steams, and afterward washes it thoroughly in running water. Then he places it for from forty to fifty seconds in a solution of brilliant yellow 0.15 Gm., concentrated sulphuric acid 10 cc., alcohol 20 cc., and distilled water 85 cc. It is again thoroughly washed and dried with blotting paper. The bacilli are colored red on a lemon-yellow background. The method is more rapid than that of Ziehl, taking exactly half the time. The tubercle bacilli are shown clearer and more numerous, thereby facilitating research. The method is just as reliable as the Ziehl-Neelsen method; there were no negative results when the Ziehl-Neelsen stain was positive.

Society Transactions

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, Oct. 13, 1932

V. H. Moon, *President, in the Chair*

Degenerative Mesa-ortitis Without Syphilis with a Dissecting Aneurysm in a Twenty Year Old Woman. Herbert Lund (by invitation).

At the age of 16 years, the patient noted that she tired quickly. Shortly after this menorrhagia developed, as well as frequent attacks of epistaxis. At the age of 18 years she was refused a life insurance policy because of high blood pressure. During her nineteenth year she had an attack of unconsciousness which was diagnosed as uremia.

The final episode in her history occurred in March, 1932, when the patient was 20 years old. After taking a walk of several miles, she felt tired and immediately went to bed. About one hour later she was awakened suddenly by a severe substernal pain. She vomited and became restless and excited.

On the patient's admission to the Philadelphia General Hospital in a critical condition her blood pressure was 196 systolic and 120 diastolic, and a peculiar bluish blanching of the left arm and leg was noted. She died shortly afterward in a severe convulsion. The only fact of interest in her family history was that her father had had hypertension.

At necropsy, a large dissecting aneurysm was found. This extended from the origin of the aorta at the base of the heart to the left external iliac artery. The intima of the aorta was ruptured 2 cm. above the aortic valve. The aorta showed advanced intimal atherosclerosis. This change was also present in the larger arteries. The heart was hypertrophied. The kidneys were small and granular.

The microscopic examination of the aorta and larger arteries showed, in addition to an advanced intimal sclerosis, marked medial degeneration. The elastic fibers were broken and scattered. Between the fibers there was a blue-staining, mucinous material. The vasa vasorum were sparse and sclerotic. Nowhere in these vessels was there any evidence of a syphilitic process. The small arteries and arterioles throughout the body showed marked subintimal proliferation, in many instances to the point of occlusion.

Although cases of dissecting aneurysm have been reported in younger persons (Rokitansky observed it in a child of 8 years), this patient was unusually young for such profound vascular degeneration.

Multiple Diverticula of the Jejunum. H. M. Dixon.

Two jejunums containing multiple diverticula along their mesenteric attachments were demonstrated. The first contained thirty-five and the second twenty diverticulations. These projected into or just to one side of the mesenteries. They varied from 1 to 3.5 cm. in diameter. The walls of the smaller diverticula contained all the coats of the intestine, while those of the larger showed no muscle. The diverticula in both cases were incidental findings at necropsy. The first specimen came from a 78 year old man and the second from a 74 year old woman.

Capillary-Like Formations in Cultures of Blood Leukocytes. W. C. Hueper.

In about 3.5 per cent of approximately 1,000 cultures of blood leukocytes in plasma, capillary-like formations were observed. Starting as small, rounded, more

or less distinctly outlined buds of leukocytes, long tubes were formed extending far into the peripheral, cell-free portion of the plasma clot. They were primarily surrounded by a delicate, clear, refractile membrane and contained in their tips a fine granular material. The leukocytes advanced from the base of the tubes into the lumens and frequently emigrated through the tube walls. Nuclei appeared in the walls of the tubes. These were small, round or oval and darkly stained by hematoxylin. In other instances, elongated, spindle-shaped cells were attached to the hyaline wall. These findings seem to indicate that leukocytes may play an active part in the production and direction of the capillary-like structures. It does not appear to be impossible that monocytes, which are derivatives of endothelial cells, may revert to histiotypic growth. This conception is supported by the observations of Huzella, who found that blood monocytes line in endothelial fashion the lumen of collodion tubes placed in blood vessels. Monocytes may, moreover, adopt in tissue cultures of leukocytes the morphologic characteristics of endothelial cells. While the causative mechanism responsible for the production and growth direction of these capillary tubes remains unknown, it seems to be likely that certain physicochemical factors present in the medium may have been active in this process in vitro as they are doubtlessly active in the developmental mechanics of capillaries in vivo. The possibility that these capillary tubes are artefacts and may have relations to cracks in the medium can be excluded, as they were never seen in cultures of other tissues.

This article is published in full in the *Archiv für experimentelle Zellforschung besonders Gewebezüchtung* (**12**:407, 1932).

THE SIZE OF THE ERYTHROCYTES IN SECONDARY ANEMIA. E. B. KRUMBHAAR.

The effect of massive hemorrhages on the blood picture of dogs was studied with special reference to the size of the erythrocyte. In one group of two dogs and a control, the test animals were bled half their determined blood volume; they showed a marked increase in the scattering of erythrocyte diameters and only a slight increase in the average cell diameter, as determined by direct measurement with the ocular filar micrometer. The calculated mean corpuscular volume was found to be slightly, but definitely, increased. In the second group, the two test animals were bled to the limit of safety; they showed a definite increase in the average cell diameter as well as an increase in "scatter." Conflicting reports in the literature indicate both increase and decrease of diameter and volume of erythrocytes after hemorrhage.

The true story of the effect of hemorrhage on the size of the red cell will, of course, eventually be forthcoming. In the meantime, it is impossible to say how much the apparent discrepancy of results should be laid to incorrect or incomplete observation (compare possible osmotic changes in plasma) and how much to the fact that different amounts of hemorrhage spread over different periods of time may produce different responses, in terms of size, on the part of the erythropoietic factor. It is easily conceivable, for instance, that a diseased bone marrow, or one undernourished as the result of long-continued secondary anemia, might put out smaller erythrocytes than a healthy marrow suddenly subjected to an extreme demand or one that after a long struggle has the balance tip to the side more favorable to regeneration. Here, too, the unexplored field of relative availability of material for stroma or for hemoglobin formation in the body might easily prove the decisive factor in the determination of size of the erythrocyte. In the further complexities of other types of human secondary anemia, conflicting responses could almost be predicted, so that generalizations about the size of the erythrocyte in secondary anemias as a group are unwarranted, and attempted classifications of anemias on the basis of size of erythrocytes are at least premature.

ROENTGENOGRAMS OF THE BREAST AND ITS LESIONS AND THEIR HISTOLOGIC CORRELATION. STANLEY P. REIMANN and PAUL S. SEABOLD.

From the age of puberty to the menopause, the breast undergoes hyperplasia and regresses in tune with the menstrual rhythm. The pathologic diagnosis of a lesion

of the breast must be considered in relation to these physiologic anatomic changes. Failure to do so leads to erroneous diagnosis and the coining of many names for one and the same process but in different stages. The present paper demonstrates the increases and decreases in the size of the breasts by roentgenograms which were taken at stated intervals before, during and after menstrual periods. The same fluctuations in size occur in conditions in which cysts appear in the breasts and also in such true tumors as periductal fibromas.

CHICAGO PATHOLOGICAL SOCIETY

PAUL R. CANNON, *President, in the Chair*

Regular Monthly Meeting, Oct. 10, 1932

PRESIDENTIAL ADDRESS: SOME CHANGING EMPHASES IN THE STUDY OF INFECTION AND RESISTANCE. PAUL R. CANNON.

Current conceptions of infection and resistance are the outgrowth mainly of investigations of the past fifty years. During this time a new science, immunology, has developed as a specialized branch of knowledge, with its own technics, journals and societies. Workers in many fields have taken part in this development, and their particular interests have determined the emphases of different periods. Thus, in the decade from 1880 to 1890, interest in etiology was dominant, and the discovery of the causative bacteria and toxins of many infectious diseases resulted from this emphasis. During the next ten years, antitoxins and humoral elements were in the foreground, although the cellular concepts of immunity, as formulated by Metchnikoff and his followers, assumed enough importance to initiate the cellular-humoral conflict. From 1900 to 1910, interest in opsonins stimulated an emphasis on vaccine therapy, while the leadership of Ehrlich encouraged a chemical trend to immunologic studies. Serologic procedures also became more prominent as they were perfected and applied generally in diagnosis. Functional methods were increasingly utilized, especially in the analysis of the phenomena of anaphylaxis. Until 1910, therefore, the emphases were predominantly etiologic, humoral, chemical, functional and serologic, whereas cellular and morphologic aspects were decidedly underemphasized. Only during the past two decades has this phase of immunity received the general attention that it deserves.

Despite the many discoveries in the field of immunity, in some respects relatively little progress has been made. Although serums for the treatment of bacterial infections have been diligently searched for since the discovery of those for diphtheria and tetanus, these two still remain the only outstandingly reliable ones. Along the paths of forty years are strewn the many failures to obtain effective serums against streptococcic and staphylococcic infections and for the treatment of such diseases as typhoid fever, cholera, dysentery, plague and anthrax. Recent achievements in the serum therapy of pneumonia, scarlet fever and erysipelas only emphasize the tortuous progress along these lines. One cannot conclude, therefore, that the therapeutic application of the notions of humoral immunity has been an unqualified success. Although the perfection of methods of purification and concentration of serums promises much for the future, many weak points are still apparent in the utilization in therapy of the principles of passive immunity.

On the other hand, the less dramatic methods of active immunization have steadily yielded results of value in the prevention of infectious disease. Such diseases as smallpox, typhoid fever, diphtheria and scarlet fever have lost many of their terrors, and probably many other infections may be as successfully controlled by immunization. A wider range of usefulness for antiserums has here been developed, especially in immunization against diphtheria and scarlet fever, with their appropriate combinations of toxin and antitoxin. Experience with these

methods has shown that active participation of the body is essential for an adequate and prolonged immunity, and the conviction has grown that the activities of the body itself determine the acquisition of increased states of resistance. Because of this belief more detailed studies are being made of the cellular mechanisms concerned, and, especially during the past two decades, pathologists and anatomists have contributed their ideas and technics to the general problem of infection and resistance.

Immunology is fundamentally a part of biology and must utilize many of the technics and concepts of the mother science. In the latter, morphology has always been the keystone, whereas in immunology there has been a danger that this phase of development might be underemphasized. For example, since 1916, only 8 per cent of the reports in the *American Journal of Immunology* and the *Zeitschrift für Immunitätsforschung* have been concerned with cellular immunity.

During the past fifty years, however, an extensive literature has accumulated pertaining to the morphologic alterations induced by the host-parasite relationship, a literature which is truly as immunologic as that of the conventional journals of immunology. In its development, the names of Metchnikoff, Virchow, Ribbert, Marchand, Maximow and Aschoff are preeminent, and it is to these and many other great morphologists that one owes the present understanding of inflammation and of tissue changes in the host resulting from the conflict with parasitic forces. The increasing emphasis of the past two decades on the activities of cells in immunity has been intensified since the appearance of Aschoff's monograph on the reticuloendothelial system. This collection and formulation of many widely scattered facts into the concept of a cellular functional system, subject to analysis by morphologic methods, have been of unusual value in focusing the attention of pathologists directly on mesenchymal cells and their relations to the mechanism of immunity. The prophetic words of Virchow, uttered in protest against the overemphasis on etiology in the 1880's, are of interest in this respect. He said (1885): "The diminutive cells for some time have fallen into oblivion. Many by the Abée-Zeiss instrument make the cells imperceptible as though covered by a cloak of invisibility and think that they no longer have consequence. But the cells are patient; they can wait; their time will come again after physicians have filled in more of the gaps in botanical knowledge. Then again the activities of the cells will enter into the front line of scientific and practical interest."

Today immunologists are interested in the origins, functions and fate of cells, and the rapidly accumulating literature bewilders. Despite the many controversies regarding cellular significance, activities and even names, the one outstanding fact is the recognition and acceptance of the principles of cellular immunity as developed by Metchnikoff fifty years ago. The genius of this great biologist was never more apparent than it is at present. Due to his influence, pathologic anatomy emerged from its descriptive phase and has became increasingly analytical. Pathologists now consider the significance, rather than the mere presence, of cells in an area of inflammation, and are searching for the ways in which phagocytic cells act defensively in infectious disease. The potentialities of the phagocytes under varying conditions, their changing forms and functional states, have aroused curiosity as to their internal metabolism. From this has come a renewed interest in antibodies, their sites of formation, and their manner of action. Jaffé recently stated that the sharp differentiation between phagocytosis and the action of antibodies, which formerly had caused so much controversy, no longer is justified, and that probably the most important outcome of all the studies on immunity and the reticuloendothelial system is that both the intracellular and the extracellular destruction of foreign material are considered as expressions of the same cellular reactions of the host.

Recent developments in the study of local immunity make these problems of more than theoretical interest, for the concentration of certain antibodies varies markedly in different organs and tissues, and this concentration may determine their protective effects. Furthermore, the agglomerating antibodies, especially as they may act prophylactically within the tissues, are probably of more importance than has been generally realized. Immune bodies may be of secondary significance

in acquired resistance, as maintained by Besredka and Metchnikoff, but until this assumption is proved, it is necessary to continue to investigate the conditions determining their sites of formation and the effects of their varying concentrations in the tissues.

It is strange that the idea of local immunity has been minimized for so long when the conditions of local infection have been so apparent. Infection and resistance are reciprocal phenomena, and certain instances of natural immunity have long been associated with the capacity of tissues to localize infection. Metchnikoff, for example, showed many years ago that the subcutaneous injection of Bacillus avisepticus into the susceptible rabbit or pigeon caused septicemia with no significant local lesion, whereas a similar injection into the insusceptible guinea-pig led to a marked local inflammation with formation of an abscess. Such therapeutic methods as the local application of antiseptics, local passive hyperemia and local application of heat have usually been employed to favor an accumulation of defensive cells and fluids at the site of infection in order to prevent dissemination of the infective agent. The early demonstrations by Fehleisen of a localized area of immunity in the skin following an attack of erysipelas have been either overlooked or disregarded. The superior efficacy of intraspinal over intravenous administration of antimeningococcic serum is further evidence of the importance of local concentration of immune bodies at the site of local infection. Experimental justification for these ideas and procedures has been furnished within recent years by numerous workers who have demonstrated areas of local immunity by various methods of immunization.

Three general methods have been used: first, nonspecific stimulation of the tissues leading to a localized accumulation of macrophages; second, localized injections of specific serums, and third, local specific active immunization.

Convincing evidence for the first type of local immunity has been presented by Gay and his students in showing a definite and constant relationship between mobilization of macrophages and resistance to streptococcic infection. Merely the local mobilization of macrophages by nonspecific means may increase by two hundred times the protective capacity of the pleural cavity of a rabbit against a virulent streptococcus. Gay spoke of such conditions as "enhanced natural resistance," and there is little question that many of the examples of local immunity reported within recent years are due largely to this nonspecific mobilization of macrophages.

Foci of increased resistance have also been obtained by local passive immunization, as, for instance, by the local intradermal injection into rabbits of antiserums to a rabbit virus and to a virulent streptococcus. In each instance, the protection conferred was superior to that secured from comparable injections of normal serum. Clark showed that the ineffectiveness of mobilized macrophages in the pleural cavity of a rabbit in protecting against pneumococci intrapleurally injected is removed by the addition to the pneumococcic suspension, before injection, of specific antipneumococcic serum. The tropinizing action of the immune serum thus facilitates phagocytosis of the pneumococci and thereby prevents their dissemination.

The third method, local active immunization, incites the local accumulation of macrophages and other cells of inflammations and to that extent secures the advantages of nonspecific stimulation; furthermore, it promotes a relatively lasting immunity and ensures whatever additional benefits may accrue from the local formation of specific antibodies. Certainly no principle of immunology has been more significant and has stood the test of experience so successfully as has that of specificity, and until one has the courage to abandon this principle and to treat such specific infections as diphtheria and tetanus with normal serum, it should be applied immunologically whenever practicable.

Opie, in studies of anaphylactic inflammation, observed the local fixation of antigen near the site of injection in animals immune to this antigen; subsequently necrosis and sequestration occurred, but the animal remained otherwise normal. He suggested that in this process "vital organs are protected at the expense of local injury." Rich questioned such a conception because of its implication that the violent inflammations of allergy are fundamentally protective. He regarded such

reactions as less protective than the more ideal indifference of immunized tissues, and did not consider them essential for definite protection. At any rate, the observations of Opie reveal new possibilities as to the manner in which the specific flocculating reactions may occur in vivo, and demand a much further study of the effects of antigen-antibody interactions in the body on the colloidal stability of tissues.

Similar reactions occur when suspensions of living staphylococci are introduced into tissues which have been immunized locally with a staphylococcic vaccine. Here, too, the micro-organisms are fixed near the site of inoculation and disseminate but slightly. Of more significance is the occurrence of agglutination of the bacteria within the immune tissues; furthermore, this agglutination is slight or entirely absent in animals which have been immunized by general methods. Therefore, concentration of antibodies in the tissues must influence the extent of the antigenic flocculation and thus impede the dissemination of the antigen from its point of entrance. The details of these experiments are described in a recent paper by Pacheco. Sullivan, Walsh and I have confirmed the morphologic observations by immunizing animals locally and demonstrating, by methods of chemical extraction, the presence of agglutinins earlier and in higher concentration in the locally immunized tissues than in those elsewhere in the body.

When living staphylococci are injected intravenously into rabbits actively immunized against staphylococci, and the liver, spleen and lungs are simultaneously excised and fixed in formaldehyde solution to which Zenker's solution has been added, bacterial stains show that the micro-organisms have been removed rapidly from the blood stream and deposited especially in the liver and spleen, where they almost immediately become swollen, adhere to the lining of the hepatic sinusoids, stain poorly and are quickly engulfed and digested by macrophages. The micro-organisms in the lungs of the same animal, however, remain small and compact, are well stained and show no evidences of having been affected by immune bodies of any sort. Such phenomena suggest again that the production of antibodies may be unequal in various organs and tissues of the body, their specific effects depending on their relative concentrations in these locations.

In all of these conditions, the relative significance of cells and of antibodies remains to be determined. Undoubtedly the local mobilization of phagocytic cells in an area of threatened infection will increase the multiplicity of contacts with the invading microbes and thus favor their engulfment and destruction. This is the most obvious explanation of the local accumulation of phagocytes in areas of inflammation. The inadequacy of such a cellular response when confronted with bacteria of superior parasitizing power, even to the point where they may continue to develop within phagocytes, does not nullify the fundamental protective significance of these cells. Metchnikoff spoke of such cells as having a veritable dyspepsia. Therefore, any measure favoring this local accumulation of phagocytic cells would seem to be theoretically sound, whether it employs specific or non-specific means, and the speed with which the cells accumulate may determine the localization and termination of an infection before it has had time to become a serious menace. The time factor in cell response may here be a matter of life or death, and the sensitivity of the involuntary nervous mechanisms is doubtless of great importance in promoting local leukocytosis. Nevertheless it is also apparent that cells accumulating under these circumstances possess only the protective properties normal for the individual host affected toward the particular bacteria concerned.

Phagocytes, however, are not the only elements which facilitate localization of infective agents; the physical and chemical properties of other tissue constituents and of the intercellular fluids may be of greater significance in promoting local fixation than has been generally suspected. Tissues unquestionably vary in their ability to adsorb and thereby to impede the passage of bacteria through them. If this adsorptive state is low, and if phagocytic cells are sparsely distributed in an area, the bacteria will be carried into the blood and lymph and become generalized. Their further fate will depend on their parasitizing powers throughout the body. On the other hand, if the tissues have a high adsorptive capacity for the bacteria

entering them, the micro-organisms may be fixed locally by an adhesive process which impairs their free passage through the tissues. Rich and McKee recently suggested these ideas and have reported experiments supporting them. They found that when virulent pneumococci were injected intradermally into rabbits which had received antipneumococcus serum intravenously some hours before, the bacteria remained localized, adhered to the tissues and did not disseminate rapidly, even in animals which had received enough benzene to bring the leukocytic content of the blood to a low level. Normal rabbits similarly treated died speedily with septicemia. This fixation of pneumococci in the passively immunized animals persisted at times for as long as forty-eight hours in the absence of any localized inflammatory exudate. It is obvious, therefore, that antibodies in the fluids and tissues, and not the inflammatory exudate, delayed the dissemination of the pneumococci. The humoral constituents, however, apparently had slight, if any, effect in restraining the growth of the micro-organisms in the leukocyte-free immune animals, and these rabbits eventually succumbed to the spreading infection.

Future investigations must reveal the conditions influencing the primary union of antigen and antibody within the tissues and particularly the part played by the flocculating reactions in hindering the dissemination of antigenic particles from the point of entrance. The reactions of the collagenic and reticulin components of the tissues must also be studied further. The experiments of Rich and his collaborators indicate that antibody proteins in the tissues specifically favor adherence of the homologous bacteria to such tissues. Presumably this antibody effect is also opsonizing through the deposition of antibody protein on the surfaces of the antigenic particles, as demonstrated so clearly by Mudd, Lucké, McCutcheon and Strumia. In this way, more effective phagocytosis and the continued localization of the bacteria are better ensured.

In all of these studies, the mutual relationships of tissues and infective agents and the complementary properties of cells and fluids are evident. Types of phagocytes, their functional states and their numbers are of significance in securing an effectively enhanced resistance. Furthermore, the supplementary action of specific immune serums or the local formation of specific antibodies reinforces the immunity mechanism. Only by a recognition of these interrelationships can one hope for progress in the application of the principles of immunology to the treatment of infectious disease.

THE TIME AT WHICH CASEIN BEGINS TO BE FORMED IN THE BREAST DURING PREGNANCY. JULIAN H. LEWIS and ORAN I. CUTLER.

The lack of species specificity of casein makes it possible to use an anticasein serum as a reagent to detect the presence of casein in tissue extracts. Boiled aqueous extracts of sixteen mammary glands of normal and pregnant heifers were precipitated at p_H 4.6, the iso-electric point of casein. The precipitates were extracted with alcohol and ether and dried. Solutions of the precipitates in saline solution were tested by complement fixation with a potent anticasein serum. Extracts of breasts from animals in the period from the twentieth to the twenty-fifth week of pregnancy gave positive tests for casein.

DISCUSSION

F. MCJUNKIN: Had acini formed in the ducts when casein appeared?

J. LEWIS: Histologic examinations were not made.

ULCUS ACIDUM OF MECKEL'S DIVERTICULUM. LESTER R. DRAGSTEDT.

A brief review of ulcer of Meckel's diverticulum is presented, with the details of a case. The patient had epigastric pain coming on from one half to three fourths of an hour after meals. At operation, a large, perforating ulcer was found in the ileum adjacent to the entrance of Meckel's diverticulum. The diverticulum was found to contain gastric mucosa of the fundus type. Following the resection, the patient made an uneventful recovery.

POTENTIOMETRIC DETERMINATIONS OF MALIGNANT HUMAN AND TRANSPLANTED RAT TUMORS. ROBERT D. BARNARD and PERRY W. ROSS.

Interest has been aroused by the differences in the electrical conductivity, dielectric constant and degree of electronegativity between malignant and nonmalignant tissues. Potentiometric measurements demonstrate a greater electronegativity in transplanted rat tumors than in the surrounding tissues.

Potentiometric measurements were made of human tissues from four sources: ulcerating malignant tumors in situ, ulcerating nonmalignant growths in situ, excised malignant tumors and excised nonmalignant tissues. The average potentials for the malignant tissues were significantly more electronegative than those exhibited by others. An analysis of the data secured by potentiometric measurements of ulcerative conditions in situ indicates that such results may have some diagnostic value.

Regular Monthly Meeting, Nov. 14, 1932

PAUL R. CANNON, *President, in the Chair*

ERYTHROPOIESIS IN LEUKEMIA. R. H. JAFFÉ.

A systematic study of the cellular composition of the bone marrow in cases of myelogenous and lymphatic leukemia discloses the constant presence of erythropoietic tissue. In myelogenous leukemia, the erythropoiesis is often so active that it approaches the leukopoiesis. In acute myelosis, it may even surpass the proliferation of the immature white cells. The erythropoiesis then draws on the most immature precursors of the red cells, namely, the erythrogonia. The anemia which is found in chronic myelosis of long standing and in acute myelosis is not due to replacement of the erythropoietic tissue by the leukopoietic tissue, but is the result of an excessive destruction of the red cells, as shown by the hemosiderosis of the blood-forming organs. In acute myelosis, the hemorrhagic diathesis aids in bringing about the rapid decrease in the number of erythrocytes.

Since hyperplasia of the erythropoietic tissue is constant in myelosis and varies only in degree, there is no reason for separating certain cases of leukemia because of the excessive neoformation of nucleated red cells.

In lymphatic leukemia, the erythropoietic tissue resists for a long time the proliferation of the lymphatic tissue.

The report will be published in full in *Folia haematologica*.

DISCUSSION

P. DELANEY: Has the urine been examined for excretion of iron?

P. CANNON: Have patients with leukemia received liver therapy?

R. H. JAFFÉ: The urine was not tested for iron. The leukemic features are not influenced by liver therapy.

COLONY FORMATION OF GREENING COCCI FROM MEASLES. RUTH TUNNICLIFF.

One of the objections to an etiologic relation of the green-producing diplococcus to measles is that a similar coccus is found in other diseases, in normal persons and in patients convalescent from measles. I have shown that opsonic experiments indicated that with one exception the greening cocci isolated before the appearance of the eruption and during the acute stage of measles formed a distinct group and were immunologically different from similar cocci isolated during convalescence and from normal persons. On this account it seemed worth while to study the green-producing colonies isolated from patients with measles with a binocular

culture microscope. The colonies were, as a rule, isolated from the nasopharynx on sheep blood agar plates. Thirty cultures were from patients with measles taken during two epidemics, and ninety-five were from normal persons and patients with tonsillitis, scarlet fever and diphtheria. Three cultures were made from patients in the preeruptive stage of measles, sixteen in the early eruptive stage, six when the rash was fading and twelve after the exanthem had disappeared. In some cases cultures were made from the same patient several times during the course of the disease. One type of colony which appeared of constant form was observed in cultures taken before the appearance of the rash and when the rash was at its height. With the fading of the exanthem this type of colony disappeared, except in two patients with complications. Similar colonies were observed only twice in the ninety-five controls.

Macroscopically, this colony appeared as a pinpoint-sized, smooth, black colony surrounded by a green zone. When examined with a culture microscope, it showed a small, round, black, conical colony with a shiny surface, surrounded by a narrow clear ring after from twenty-four to forty-eight hours' incubation. This clear ring was not due to hemolysis, because it was also observed around colonies on plain and chocolate agar, but it gave the impression that it was caused by partial depression of the colony in the agar. The top of the colony was soft and easily removed, leaving a rough surface. After from twenty-four to forty-eight hours' incubation, the colony increased in size, lost its dark appearance, became flattened and showed more or less parallel markings, perpendicular to the margin. With increase in size of the colony the clear ring often became less apparent. The surface now became friable, and the surrounding agar appeared smoother and raised above the surface. This swollen appearance of the medium was also observed around colonies of greening cocci from other sources. The center of the colony now showed signs of partial division, and later indentations appeared in the margin, giving the appearance of a rosette. The edge became irregular and appeared lobulated and finally, after from three to fourteen days, formed a hard, smooth, shiny colony with four or more lobules lying half raised and half below the surface of the medium to which it was adherent. All colonies did not reach the lobulated stage.

Subcultures from colonies in any of these stages of development began growth again as small, depressed, conical colonies. The organisms from these colonies appeared as gram-positive, small, round or slightly elongated cocci in pairs or fours on solid mediums and as pairs and short chains in fluid mediums. Cocci from the depressed colonies were virulent for mice and produced a rash in the skin of rabbits when injected intravenously, while those from lobulated colonies were avirulent for mice and did not cause an eruption.

Large, flat, dull colonies with irregular lacy edges and smooth, convex and smooth, conical colonies could be dissociated and stabilized from rough and smooth outgrowths from the various stages of development of the depressed colony, except rarely from the lobulated colony.

Rough colonies showed gram-positive and gram-negative, large, swollen cocci with pointed ends, in pairs and chains, and many large bacillary and filamentous forms. The organisms from rough colonies were avirulent for mice.

Tiny G colonies, the gonidial colonies of Hadley, Delves and Klimek, were dissociated from cocci in one culture of a depressed colony. They appeared as minute, adherent, light, granular, irregular, slowly greening colonies. They often gave the appearance of budding off from the flattened edge of the depressed colony, which they sometimes encircled. The G colonies were difficult to stabilize, developing, often quickly, into larger, depressed, conical colonies. They were present in the culture before filtration and were recovered from V filtrates, but so far not from N filtrates. The organisms from the G colonies appeared as diplococci just visible to diplococci about half the normal size.

Cultures from three patients taken before the appearance of the rash showed only depressed, conical colonies with or without some of the variations. In one instance, G colonies were observed in the preeruptive stage. With the onset of the eruption and during convalescence various other greening colonies appeared

on the blood agar plates. Those most frequently found were: smooth or granular convex colonies; slightly granular or smooth conical colonies; flat, granular colonies with a central peak; large, moist, smooth convex colonies; pebbly convex colonies, and rough conical colonies with lacy edges. Some of these colonies may have been dissociants of the depressed colony, just as during the course of scarlet fever colonies typical of scarlatinal streptococci were found associated with other types of hemolytic colonies, which appeared to be their dissociants.

So far neither the dissociants of the depressed colony nor the cocci from colonies found during convalescence from measles have been reverted to depressed, conical colonies.

By the opsonic test the cocci from the depressed colony in its various forms belonged to the measles group of diplococci, but not those from its rough and smooth dissociants and from the other greening colonies found during the course of measles. The diplococci from depressed colonies isolated from two controls did not opsonify like the measles group and were not virulent for mice.

DISCUSSION

I. PILOT: I have studied similar changes in the hemolytic varieties of streptococci. Have you found any large, moist colonies with capsulated cocci? These were seen during the influenza and then later disappeared. Are morphologic changes connected with variations in virulence?

E. PRIBRAM: Are there any anaerobic forms of streptococci in measles?

R. TUNNICLIFF: I found large, moist colonies only once, but not as large as those described by Mathers. The organisms were isolated in blood cultures anaerobically, but subsequent generations grew aerobically.

THE COPPER AND "ACTIVE" IRON CONTENT OF TISSUES. ARTHUR LOCKE and D. O. ROSBASH.

Determinations of total iron and iron extractable by 10 per cent trichloracetic acid after preliminary saturation with air, carbon monoxide and nitric oxide, respectively, have indicated the presence in respiring tissue of a kind of iron not derived from hemoglobin or cytochrome and distributed, in the tissues, in amounts proportional to the intensity of the metabolic processes supported.

The probable existence of four biologically different kinds of copper is suggested: hematocyanine, present in the blood of invertebrates of the type of the lobster and octopus, noncatalytic and concerned in the oxygenation — not the metabolism — of tissue; anionic, cuprous copper, present in the anaerobic bacteria and motivating metabolism in the exclusion of air through the maintenance of a heightened reducing potential; diffusible, cationic copper, perhaps found in seeds and in the spores of bacteria, capable of combining with and neutralizing the active reducing centers and of inhibiting metabolism; and cationic copper, embedded in the protoplasm and behaving toward similarly embedded anionic iron as the oxidizing electrode of an electrolytic cell behaves toward the reducing electrode. The latter type of copper may be the principal one present in uninjured respiring mammalian tissue and may be concerned in the motivation of cellular respiration.

The amount and proportion of copper and active iron found in the tissues of normal and sarcomatous chickens and of normal cabbage-fed and thyroid-fed rabbits were directly related to the intensity and balance of the metabolic processes supported. The active metal content of the liver was twelve times that of the unpigmented portions of the skeletal musculature. The proportion of copper to iron in the brain and heart was three times that found in the liver, kidney and muscle, and four times that found in the Rous sarcoma. (The metabolic processes of the brain and heart are more exclusively devoted to the support of respiration than those of the liver, kidney and muscle. Those of the Rous sarcoma are partially devoted to the support of respiration.)

Abnormally low copper levels were produced in the tissues of growing rabbits maintained on cabbage. The lowered levels were accompanied by weakness and

increased susceptibility to infection. While the lowered levels in the liver were compensated by an increase in the weight of that organ, the lowered levels in the heart were accentuated by a decrease in total weight. A parallel relation was observed in sarcomatous chickens.

The copper lost from the tissues of thyroid-fed rabbits as the result of emaciation does not appear to be excreted, but may be retained almost entirely in the blood plasma. The copper levels in the plasma of chickens kept in air containing carbon monoxide were doubled as the result of a 50 per cent decrease in plasma volume. Iron was not similarly conserved.

ENTEROGENOUS CYSTS AND DIVERTICULA. G. MILLES and H. O. PONCHER.

The group of cysts and diverticula of enterogenous origin which because of their position and relation to the intestine can be separated from the classic Meckel's type finds illustration in the following case.

A white boy at the age of 18 months had violent cramplike abdominal pain. These attacks recurred at irregular intervals, sometimes associated with stools bright red with blood. During the third year the hemorrhages had caused marked anemia and weakness. A roentgenogram of the chest revealed a large globular mass in the right side, displacing the heart to the left, with a defect of the vertebral bodies from the fourth to the seventh. The mass was resistant to x-ray therapy, and the patient died following its removal.

Necropsy.—Post mortem, a second cystic mass was discovered in the mediastinum. It was filled with thin serous fluid containing many cholesterol crystals. Also a diverticulum was revealed lying between the leaves of the mesentery and rising 20 cm. above the ileocecal valve, communicating with the small intestine here and by a second opening about 10 cm. above. There was a superficial ulceration at the margin of the first communication. In character, the diverticulum simulated grossly the small intestine, except in its distal 8 cm., where a polypoid mass was present, and beyond this two incompletely separated cysts. It measured 51 cm. in length and lay in close approximation to the small bowel throughout its course except at the distal 8 cm., where a small segment of mesentery intervened.

Microscopically, the cysts of the chest consisted of gastric tissues, the mucosa being preserved in one area and simulating the pyloric tissue. The wall of the diverticulum corresponded to mucosa of the small intestine in its microscopic picture, and the polypoid mass near the terminus corresponded to gastric mucosa. The epithelial nodes of Lewis and Thyng found in embryos of from 5 to 42 cm. by several authors seem to explain best the embryologic origin of the anomalies described here.

Book Reviews

The Cardiac Output of Man in Health and Disease. By Arthur Grollman, Ph.D., M.D., Associate Professor of Physiology in the Medical School of the Johns Hopkins University. Price, $4. Pp. 324, with 25 figures. Springfield, Ill.: Charles C. Thomas, 1932.

In an authoritative manner the writer has brought together in a monograph what is at present known about the cardiac output of man in health and in disease. Although more than three hundred years have elapsed since Harvey described the circulation of blood, it has been only in recent years that accurate measurements of the cardiac output in man have been possible. It is particularly fitting that one who has made eminent contributions to this subject should have written this monograph.

Chapter 1 opens with a historical introduction followed by descriptions of the methods of measuring the cardiac output in man, the principles on which these methods are based and comparisons of the results obtained by use of different methods. Detailed description is given of the technic of the acetylene method which the author devised. Proofs of the validity of this method and data showing that the results obtained by its use are in agreement with those obtained simultaneously by the direct method are then presented. The author is deeply cognizant of the limits which circumscribe his method and warns against its use when it is unwarranted and in subjects in whom the conditions on which the method is based cannot be fulfilled.

The physiologic variations of the cardiac output are next discussed—changes that occur as a result of change in posture, of sleep, of the menstrual cycle, of temperature, of mild exercise, of altitude and of the ingestion of food and fluids. Perhaps one of the most important contributions of the author is what appears now to be a fact, that the cardiac output of normal man under basal conditions is a function of the body surface, just as is the oxygen consumption, and that it is predictable for normal persons. He has introduced the term "cardiac index," meaning by this concept the cardiac output in liters per square meter of body surface.

In a discussion of the application of studies of cardiac output to pharmacology and therapeutics, the effects on the cardiac output of many drugs, including alcohol, caffeine and digitalis, are described; all of these are of particular interest to the clinician. The author emphasizes wisely that the effect of a drug may be different when given to man in a so-called normal state and when given to one in the morbid state, although the fundamental action of the drug is the same in the two states. He then assembles what is known about the cardiac output in morbid states—those primarily cardiac as well as those not primarily involving the circulatory system. The book is brought to a close with a section of several chapters in which the cardiac output is correlated with the other physiologic functions of the organism as a whole—the metabolism, the pulse rate, the velocity of the blood flow, the arterial and the venous blood pressure and the size of the heart, ending with an excellent chapter on the regulation of the circulation.

Those who have been interested in this particular field of investigation have been fully aware of the vast avenue of approach to the study of the circulation opened by the introduction of the acetylene method of measuring the cardiac output of man and also of Dr. Grollman's contributions to cardiac physiology and pathology through its use; nevertheless, the breadth of his accomplishments was hardly brought into its true perspective until the knowledge we have on the cardiac output was brought together in this volume, for he has made contributions in almost every province that he discusses. Indeed, Dr. Grollman has made fundamental contributions to the elucidation of the problems of the circulation. The book also reveals the wide gaps in knowledge of the cardiac output.

Dr. Grollman has written an admirable book. The data and the discussions are logically presented. The author has thought concisely and clearly. With the authority based on experience, he has evaluated the methods for measuring the cardiac output. The book is written in an interesting fashion and reads easily; discussions difficult in context are written clearly. It is enthusiastically recommended to all physicians and students, for the fundamental data presented and principles discussed are too broad to be of interest only to physiologists and those concerned with cardiac diseases.

The style is good, and the publishers have given Dr. Grollman's book an excellent presentation.

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PHYSICAL CHEMISTRY FOR STUDENTS OF BIOLOGY AND MEDICINE. By David I. Hitchcock, Ph.D., Associate Professor of Physiology in the Yale University School of Medicine. Price, $2.75. Pp. 183. Springfield, Ill.: Charles C. Thomas, 1932.

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